Efficacy of Different Treatment and Management Types for Phantom Limb Pain

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A Critical Literature Review submitted in partial fulfillment of the requirements for the Senior Research Thesis
Abstract

Phantom limb pain affects an alarming amount of amputees. Little is known about the true cause of phantom limb pain, making it difficult to establish a standard treatment for it. This literature review looks at the etiology of phantom limb pain as well as the three major forms of treatment for phantom limb pain: pharmacological, invasive, and supportive. These three forms of treatment use different methods to counter a common occurrence in phantom limb pain, which is cortical reorganization. Advantages, disadvantages, and the overall efficacy of each treatment are also included.
Introduction

A large body of literature states that phantom limb pain (PLP) is a form of neuropathic pain that affects 50% to 80% of amputees. Phantom limb pain is the perceived pain that amputees experience in amputated limbs (Hsiao et al., 2012). Despite the fact that PLP was first documented in the 1600s, scientists still do not know what exactly causes PLP, nor is there one standard treatment for PLP. This paper focuses on the three major treatments used in the treatment of PLP: pharmacological, invasive, and supportive.

Pathway

Generalized pain receptors called nociceptors fire when something comes in contact with the skin that is outside the temperature range of thermoreceptors, or when the thresholds of the mechanoreceptors have been exceeded (Wolfe, Levi, Bartoshuk, Lederman, and Merfeld, 2012). Pain signals are sent along the spinothalamic pathway from the nociceptors in the skin along small unmyelinated neurons into bundles of axons between spinal cord segments that correspond to receptive fields on the body (Wolfe et al., 2012). That signal then crosses over upon entry into the spinal cord and moves to the dorsal horn of the spinal cord, through the ventral posterior nucleus of the thalamus, and up in to the contralateral somatosensory cortex located behind the central sulcus (Wolfe et al., 2012). The somatosensory cortex is organized by bordering body areas or dermatomes that vary in threshold and sensitivity (Wolfe et al., 2012). This variance is due to the magnification factor in which the larger area of the somatosensory cortex that a dermatome covers, allows for more CNS processing and better perception of details (Wolfe et al., 2012). A disruption of this pathway, like an amputation would create a disconnect between the periphery and the somatosensory cortex.

Etiology
There are many different theories regarding the mechanisms and causes of PLP. The dominant medical model for PLP is that the pain is generated by aberrant peripheral afferent nociceptive signals that originate from severed and swollen nerve endings in the stump, known as neuromas (Leskowitz, 2014). In these neuromas there is an increased buildup of molecules that heighten the expression of sodium channels, which leads to a hyperexcitability and spontaneous discharges (Soin, Shah, and Fang, 2014). This hyperexcitability and spontaneous discharges cause repeated afferent signals to become centrally generated despite the absence of significant peripheral input causing those who experience PLP to become more sensitive and to experience more pain despite less stimulation or provocation (Leskowitz, 2014). Under this theory, second amputations have been performed to remove neuromas, but this has only caused additional pain and the development of new neuromas (Jerath, Crawford, and Jensen, 2015). Under the neuroplasticity/cortical reorganization model, PLP is classified as a type of neuropathic pain that is the consequence of segregation between visual feedback post amputation and the cortical representation of the amputated region in the somatosensory cortex (Mercier & Sirigu, 2009). This conflicting cortical information results in sensations of pain. Particularly in unilateral, upper limb amputations there has been evidence of cortical reorganization in which neighboring regions in the somatosensory cortex encroach and take over the region of the amputated limb (Leskowitz, 2014). This cortical reorganization is thought to generate irregular sensations of pain as a result of the amputee’s central nervous system’s attempt to reestablish homeostasis after the previous sources of afferent input are lost (Leskowitz, 2014).

Section I: Pharmacological Treatment Strategies

The most common forms of treatment for PLP are pharmacological treatments that are used on the basis that PLP is the product of aberrant peripheral afferent nociceptive signals that
originate in neuromas at the amputation stump and that persist due to central sensitization (Leskowitz, 2014). Abiding by this theory, pharmacological forms of treatment work at the level of neurotransmitters and receptors in the central nervous system to dampen central sensitization and produce an analgesic effect (Leskowitz, 2014). Opioids, which are effective in their treatment of nociceptive pain, have also been used to treat chronic or neuropathic pain like PLP, but with more controversial results (Huse, Larbig, Flor, and Birbaumer, 2001). A study conducted by Huse, Larbig, Flor, and Birbaumer (2001) sought to test the analgesic effects of an opioid medication MST, an oral retarded morphine sulfate, on treatment-resistant PLP patients. This hypothesis was tested with twelve participants in a randomized double-blind placebo controlled crossover design that investigated the efficacy of MST compared to a placebo in two identical 4-week treatment phases that took place after a 4-week baseline phase (Huse et al., 2001). Doses of MST were titrated individually and a one to two week wash out phase with gradual substance reduction separated the two treatment phases (Huse et al., 2001). Results show that participants experienced significantly less pain during the MST phase than during the baseline phase or the placebo phase and that there was no significant difference between the baseline phase and the placebo phase (Huse et al., 2001). The drug, MST proved to be more effective than the placebo in producing analgesia (Huse et al., 2001). Results also show that PLP and cortical organization are positively correlated with cortical reorganization being more drastic with more intense perceptions of PLP, by comparing participants’ pre-assessment phase MRIs and VAS ratings with their MRIs and VAS ratings after MST and placebo phases (Huse et al., 2001). These MRI comparisons also show that MST helps to reduce PLP as well as cortical reorganization, with MRIs taken after the MST phase showing less cortical reorganization than MRIs taken during the pre-assessment phase and placebo phase (Huse et al., 2001). Huse et al.
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(2001) recognize that their results support their hypothesis that retarded morphine sulfate, MST, leads to significant pain reduction compared to the placebo, but they also acknowledge that the double-blind component of their experiment failed because participants and doctors were able to differentiate between the placebo phase and the drug phase. Huse et al. (2001) also realized that participants were experiencing additional responses (dizziness, tiredness, constipation) to MST at follow-ups after the study, suggesting that the titration of doses should be performed gradually so as to prevent side effects. This study did much to support the efficacy of opioids on PLP and cortical reorganization, but it also raised questions regarding the side effects of opioids.

A case study conducted by Kumar et al. (2015) observed the effects of opioids on a 72-year-old below the knee amputee’s PLP. For postoperative pain the patient was administered epidural morphine 3mg twice a day for five days and he was pain free for those five days. Upon discharge the patient was prescribed oral morphine 5mg four hourly, paracetamol 1000mg six hourly, and Bisacodyl 10mg at bedtime. The patient had severe complaints of pain and rated that pain at an 8 out of 10 on the VAS after one week (Kumar et al., 2015). After this complaint doctors started the patient on oral morphine 10mg four hourly, which needed progressive upward titration to 120mg four hourly over a period of four weeks (Kumar et al., 2015). Once the patient’s PLP rating dropped to 1-2 on the VAS, the patient was maintained on monthly follow-ups for the next year with a stable oral morphine dose (Kumar et al., 2015). However, after a year of stability the patient complained of increased pain that required an increase in the dose of oral morphine gradually to 300mg four hourly and the patient reported his PLP at a 4 on the VAS (Kumar et al., 2015). The patient’s pain was not controlled adequately and required epidural analgesia with 0.125% bupivacaine infusion for pain relief, which was adequate for PLP relief (Kumar et al., 2015). Any attempts to wean the dose of oral morphine resulted in rebound pain
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and features of opioid withdrawal (Kumar et al., 2015). Kumar et al. (2015) posit that their patient had intermittent breakthroughs in PLP that required progressive dose escalation, but also raised their patient’s chances of experiencing opioid-induced hyperalgesia (OIH), a paradoxical response to opioids in which the patient can become more sensitive to painful stimuli. This case study conducted by Kumar et al. (2015) echoes some the same concerns about opioid use in the treatment of PLP that were brought to light in the study conducted by Huse et al. (2001).

Another group of drugs that have been used for the treatment of PLP are N-methyl-D-aspartic acid (NMDA) receptor antagonists, which reduce constant pain, allodynia and pathologically decreased pain thresholds at NMDA receptor sites that help to mediate cortical reorganization and hyperexcitability in dorsal horn neurons after deafferentiation (Maier et al., 2003). The most powerful NMDA-receptor antagonist, ketamine, has been effective in the treatment of neuropathic pain, but has also been shown to have unpleasant side effects (restlessness, hallucinations, anxiety disturbances) that make it less feasible (Maier et al., 2003). Memantine, which is the derivative of amantadine, is a less powerful NMDA-receptor antagonist that has been effective in the treatment of other chronic disorders was the focus of a study conducted by Maier et al. (2003) who executed a placebo-controlled study with a daily dose of 30mg memantine in 36 amputees with chronic PLP. Participants rated their PLP intensity using the numeric pain scale (NRS) daily in a pain diary (Maier et al., 2003). PLP intensity decreased significantly for both the placebo group and the drug group compared to baseline, which was assessed prior to study entry (Maier et al., 2003). Other than the first day of titration there were no significant differences between the placebo group and the drug group for the remaining 4 weeks of the study (Maier et al., 2003). The findings of Maier et al. (2003) show that the NMDA-receptor antagonist memantine at the daily dose of 30mg was not clinically effective in
the treatment of PLP. Wiech et al. (2004) replicated the study conducted by Maier et al. (2003) in terms of experimental design, drug (memantine), and drug dosage (30mg/day) and had similar results on the basis that there were no significant differences between the baseline phase, placebo phase or memantine phase. The findings of Wiech et al. (2004) assert that memantine at 30mg/day has no clinical effect on PLP intensity. There were no reports of negative side effects to the drug in either study, which suggests that testing the efficacy of a higher dose could yield different results. However some researchers believe that memantine’s lack of effect on PLP is not a matter of dosage, but instead matter of the mechanism itself (Maier et al., 2003). While mechanisms that are mediated by NMDA receptor activation, such as rapid cortical neuroplasticity and hyperexcitability in dorsal root neurons, are likely necessary to provoke plastic synaptic changes in both the central and peripheral nervous systems, those neuroplastic changes may already be fixed making NMDA-receptor antagonist useless (Maier et al., 2003).

Schley et al. (2007) sought to further investigate the effects of the NMDA-receptor antagonist memantine on early PLP, since previous studies have suggested that NMDA-receptor antagonists are ineffective on chronic PLP. Schley et al. (2007) observed the effects of memantine by conducting a randomized double-blind experiment in which all participants received a continuous brachial plexus block for the first week. This continuous brachial plexus block (CBPB) was accompanied by 10mg of memantine for the treatment group or 10 mg of the placebo for the control group (Schley et al., 2007). During the second week the CBPB is discontinued and the dosages for both the memantine group and the placebo group is increased to 20 mg (Schley et al., 2007). For the third and fourth weeks the dosages were increased to 30 mg for both groups. For the duration of the experiment participants documented any adverse effects to the drug (nausea, dizziness, fatigue, headache) as well as their pain ratings using the VAS,
three times a day in their pain diaries (Schley et al., 2007). Schley et al. (2007) found that the combined use of the continuous brachial plexus block and memantine soon after amputation can prevent the development of PLP for amputees not already suffering from chronic PLP. Pain intensity rated using the VAS was significantly lower for the memantine group than the placebo group for the first six days post surgery, suggesting that while the CBPB does have an analgesic effect, memantine has additional analgesic effects that in combination with the CBPB provide more pain relief than the CBPB alone (Schley et al., 2007). Intensity of phantom pain rated using the VAS was significantly lower for the memantine group than the placebo group at both four weeks and six months post-amputation (Schley et al., 2007). However after six months PLP intensity increased for participants in the memantine group such that there was no significant difference between the memantine group and the placebo group. The findings of Schley et al. (2007) support the findings of both Wiech et al. (2004) and Maier et al. (2003) on the basis that memantine is effective at the onset of PLP allowing it to be useful in PLP prevention, but ineffective in the reduction of chronic PLP.

Other medications that have been effective in treating neuropathic pain are duloxetine (DUL) and pregabalin (PGN) (Spiegel, Lappinen, and Gottlieb, 2010). DUL increases the presence of norepinephrine (NE) and serotonin (5-HT), both of which have been shown to decrease in patients suffering from PLP (Spiegel et al., 2010). PGN, a successor of gabapentin, is related structurally to GABA, but does not produce its effects through the GABA receptor complex (Spiegel et al., 2010). Spiegel et al. (2010) completed a case study, observing the effective treatment of PLP using both DUL and PGN. The patient was a 49-year-old female below the knee amputee who complained of depression and described her PLP as a burning sensation that originated in her phantom right heel and toe (Spiegel et al., 2010). Prior to
beginning treatment the patient rated her PLP at a 7 out of 10 on the VAS (Spiegel et al., 2010). The patient started on medication regimen of DUL 30mg qAM for mood/PLP and PGN 50mg TID for PLP, while also receiving 8mg/day of morphine sulfate (MS) (Spiegel et al., 2010). After four days of treatment, DUL was increased 60mg qAM and PGN was increased to 100mg TID, but MS was decreased to 5mg/day (Spiegel et al., 2010). On the eighth day the patient rated her PLP at a 5 out of 10 on the VAS and her MS was decreased to 2mg/day, but PGN was increased to 150mg qAM and 300mg qHS (Spiegel et al., 2010). After twelve days of treatment patient rated her PLP at a 3 out of 10 on the VAS and MS was discontinued (Spiegel et al., 2010). While the patient’s PLP and depression did appear to be affected by her DUL and PGN regimen, Spiegel et al. (2010) assert that it is unclear whether her mood improved as a result of decrease in PLP intensity or the antidepressant effect of DUL and vice versa for the patient’s decreased PLP intensity. Spiegel et al. (2010) also posit that both DUL and PGN could have been effective in alleviating PLP on their own. The complete efficacy of DUL and PGN is also unclear because the patient was also taking MS for postoperative pain (Spiegel et al., 2010). In order to fully test the efficacy of DUL and PGN on the reduction of PLP a proper experiment with multiple subjects and a placebo control should be conducted.

Another dual medication treatment is buprenorphine/naloxone therapy, which is a mixed opioid agonist-antagonist that has been used as an alternative to opioid analgesics for chronic pain and is used by those who wish to cut down on side effects evident with pure opioid agonists (Licina, Hamsher, Lautenschager, Dhanjal, Williams, and Spevak, 2013). Buprenorphine is a mu agonist as well as a kappa and delta agonist, while naloxone is a mu antagonist with no oral bioavailability, meaning that it cannot be absorbed into the circulatory system orally (Licina et al., 2013). The combination of buprenorphine and naloxone can prevent intravenous abuse
because naloxone can stop the buprenorphine’s mu agonist effects (Licina et al., 2013). Licina et al. (2013) conducted a case series observing four patients who began buprenorphine/naloxone treatment after other pharmacological treatment proved to be ineffective in the management of their PLP. Three of the four patients were bilateral transfemoral amputees while one was unilateral transfemoral amputee, all resulting from traumas (Licina et al., 2013). All patients rated their PLP as at least an 8 on the VAS at the beginning of buprenorphine/naloxone therapy with all of them starting at a dosage of buprenorphine/naloxone 8mg/2mg (Licina et al., 2013). As therapy continued, patients were able to decrease and eventually discontinue all other pain medications and adequately manage their PLP with just buprenorphine/naloxone (Licina et al., 2013). Out of the four patients, two of them experienced complete resolution of PLP while one rated his PLP at a 3 out of 10 and the other rated his PLP at a 2 out of 10 and also reported that he no longer experienced cravings for medications (Licina et al., 2013). The outcomes of this case series suggests that the use of mixed opioid agonist-antagonist medication is an appropriate alternative to pure opioids as well as an appropriate form of therapy when opioids are not sufficient in controlling neuropathic pain (Licina et al., 2013).

Pharmacological treatments sought to prevent or stop cortical reorganization by attacking the problem at the neurotransmitter level. The most common of those treatments are the opioid treatments, which have been shown to be effective in the treatment of neuropathic pain, but have had less decisive results for neuropathic pain (Licina et al., 2013). In the studies previously mentioned studies, even when opioid treatments proved to be mildly effective, the patients on those opioid medications often had to increase their dosage over time (Kumar et al., 2015). Participants also experienced withdrawal symptoms when the titration of the opioid medications was not gradual enough (Huse et al., 2001). Another drug type that was tested in the treatment
of phantom limb pain was the NMDA-receptor antagonist memantine, which have been shown to mediate central sensitization processes (Wiech et al., 2004). Researchers found that while NMDA receptor sites are important in the onset of cortical reorganization, once it has fully set in the manipulation of these receptor cites is ineffective (Maier et al., 2003). The most effective form of pharmacological treatment was the dual treatment buprenorphine/naloxone regimen, which combined a mu agonist and a mu antagonist providing the pain relief of an opioid medication without the adverse effects of opioid medication (Licina et al., 2013).

**Section II: Invasive Treatment Strategies**

Theories concerning the mechanisms of phantom limb pain can be separated into three distinct yet interconnected groups: peripheral, spinal, and central (Bittar, Otero, Carter, and Aziz, 2005). In the periphery, deafferentation causes deterioration of the distal peripheral nerve and neuromas from the surviving proximal nerve section that can generate abnormal discharges may aid in the maintenance of pain (Bittar et al., 2005). While physically stimulating the neuromas can increase PLP, that pain cannot be alleviated by creating a conduction nerve block (Bittar et al., 2010). At the spinal level, the receptive fields of the spinal cord can reorganize, and this often occurs after a peripheral nerve injury (Bittar et al., 2005). In the event of a peripheral nerve injury, central hyperexcitability occurs, which is mediated by NMDA receptors and their transmitter glutamate (Bittar et al., 2005). At the central level the primary somatosensory cortex undergoes structural and functional changes after an amputation due to the sprouting of neurons from neighboring regions into the deafferented region (Bittar et al., 2005). It is also thought that the more sprouting and reorganization that occurs, the more intense the PLP is (Bittar et al., 2005).
A clinical study conducted by Bittar, Otero, Carter, and Aziz (2005), presents the results of continuous deep brain stimulation (DBS) in three patients suffering from PLP. Patients were instructed to keep a daily pain diary pre- and post-surgery in which they rated the intensity of their PLP using the visual analog scale (VAS) (Bittar et al., 2005). Using a combination of MRI and CT scans as a guide and a stereotactic arc deep brain stimulation electrodes were inserted into the contralateral periventricular gray (PVG) and sensory thalamus (Bittar et al., 2005). Once proper location, frequency, voltage, and pulse width were determined to provide the appropriate pain relief, temporary lead extensions were externalized in order to do further testing postoperatively and then a subcutaneous pulse generator was implanted in to the pectoral pocket of the patient (Bittar et al., 2005). All patients were assessed every three months after surgery and it was reported that all patients achieved adequate PLP relief (Bittar et al., 2005). Opioid intake was also reduced for the two patients that required morphine after surgery (Bittar et al., 2005). The results from this small sample size case study show that continuous DBS was effective in the alleviation of PLP (Bittar et al., 2005). In order to truly determine whether deep brain stimulation is effective in the treatment of PLP, more data on the subject should be gathered. A study conducted by Pereira et al. (2013) evaluated the outcomes of twelve different cases of DBS of PLP amputation. The procedure of this study replicated that of the study conducted by Bittar et al. (2005) in terms of DBS surgery, implantation, and rating of pain (Pereira et al., 2013). There was a significant PLP improvement with DBS both initially and after 12 months, suggesting that DBS can provide analgesia on a consistent basis for amputees suffering from PLP with continued improvements at twelve months (Pereira et al., 2013).

Utilizing a treatment at the spinal level, Eldabe et al. (2015) conducted a study to evaluate the efficacy of dorsal root ganglion (DRG) stimulation in the treatment of PLP. Patients
were implanted with quadripolar neurostimulation leads using an epidural approach and stimulant contacts were placed near relevant DRGs based on individual pain distributions (Eldabe et al., 2015). After implantation, baseline PLP information was recorded (site of pain, duration, management strategies) and pain intensity was rated using the VAS, and the same information was recorded at follow-up appointments (Eldabe et al., 2015). Results asserted that neuromodulation of the DRG has a positive effect on PLP and that further research is needed to fully understand the how important things are at the DRG for the development and maintenance of PLP (Eldabe et al., 2015).

Focusing on the peripheral mechanisms of PLP, Rauck et al. (2014) conducted an experiment with the hypothesis that selective stimulation of target sensory fibers can be achieved by using a single-contact electrode lead placed remote from the nerve trunk. This hypothesis was tested by implanting a fine-wire lead percutaneously under 0.5-3.0cm away from the sciatic or femoral nerve of the patients (Rauck et al., 2014). Once correct lead placement was confirmed by eliciting a comfortable paresthesia in the painful area without eliciting muscle contractions, participants began the two-week home trial (Rauck et al., 2014). To prepare for the home trial the lead was coiled outside the skin in order to create a strain-relief loop that was then covered with waterproof bandages (Rauck et al., 2014). Participants were seen at follow-up assessments at the conclusion of the home trial, one week after the home trial, and four weeks after the home trial (Rauck et al., 2014). Out of the sixteen participants who took part in the home trial, two reported no paresthesia or pain relief (Rauck et al., 2014). One reported that the stimulation was painful while the other reported no sensation during stimulation (Rauck et al., 2014). The remaining fourteen participants responded to the stimulation and reported paresthesia coverage of the painful area as well as clinically meaningful pain relief (Rauck et al.,
2014). Of those who successfully completed the home trial, one participant accidentally pulled out his lead five days into the trial and had to get it re-implanted (Rauck et al., 2014). The results of this study suggest that peripheral nerve stimulation can be an effective form of treatment for PLP, with the majority of the participants experiencing paresthesia coverage over the painful region, but with the complications noted above this does not seem like a feasible form of treatment due to the level of upkeep needed on the side of the patient (Rauck et al., 2014).

Another study that focuses on the peripheral mechanisms of PLP that was conducted by Soin, Shah, and Fang, (2014), sought to test the analgesic effect of a high-frequency electrical nerve block on the severed nerves in amputees suffering from PLP. Soin et al. (2014) tested this by implanting a cuff electrode around the sciatic or tibial nerves of seven lower limb amputees and then using an external waveform generator and eventually an implantable generator, applying sinusoidal waveforms of 10kHz up to 10V for 30 minutes during each participant-initiated treatment session. Participants rated their PLP intensity using the numeric rating scale (NRS) and participants were required to return to the clinic weekly and then monthly for follow-up assessments where pain diaries were assessed and reviewed (Soin et al., 2014). The results of this study assert that electrical nerve blocks can reduce the PLP intensity in amputees who suffer from chronic PLP (Soin et al., 2014). Primary findings also suggest that PLP is not only reduced during treatment, which occurs when the participant feels pain, but also for minutes and even hours after the cessation of treatment (Soin et al., 2014). While these results are promising, for future studies it would be interesting to see if this treatment is effective for upper-limb amputees as well.

A lesser-known form of PLP treatment is cryoanalgesia, which has been used as a long-term treatment for other forms of chronic pain (Moesker, Karl, and Trescot, 2014).
Cryanalgesia works by applying cold to nerves, which creates a conduction nerve block that is similar to the effect of local anesthesia (Moesker et al., 2014). This treatment has such long-lasting pain relief because ice crystals damage the *vasa nervorum*, which are small arteries that supply blood to interior parts of peripheral nerves (Moesker et al., 2014). This damage of the *vasa nervorum* causes severe endoneural edema and deterioration of the nerve (Moesker et al., 2014). Researchers Moesker, Karl, and Trescot (2014) sought to assess the role of peripheral nerves in maintaining PLP and the use of cryanalgesia by recruiting five participants all who described their PLP as burning pain. Participants also reported the movements of their amputated limbs (Moesker, Karl, and Trescot, 2014). Participants were required to give details reports as to where they felt the pain originated in their phantom limb and from there doctors pinpointed the remaining proximal portion of the corresponding nerve by palpation on the distal portion of the stump (Moesker et al., 2014). A neurostimulator was then used to locate the most distal portion of the remaining nerve and cryanalgesia was then performed at that location using 2 cycles of 3-minute freezing to -70 degrees Celsius, separated by a 2-minute defrost (Moesker et al., 2014). Of the five participants in this study, three reported excellent outcomes (90%-100% decrease in pain); one participant reported an acceptable outcome (40% decrease in pain); and one participant reported a 20% decrease in pain (Moesker et al., 2014). One participant remained pain-free after two and a half years and two participants reported 90% to 95% improvement at five years, while the remaining two participants died after five months, with pain relief until death (Moesker et al., 2014). While this was an extremely small sample size, the results from this study suggest that this form of treatment could be highly effective for many amputees suffering from chronic PLP.
Invasive treatments aim to counteract cortical reorganization by applying nerve stimulation or nerve blocks to the affected nerves in the periphery or in the spinal column. The use of electrical currents to create conduction blocks in motor, sensory, and autonomic nerves has been used to treat amputees with PLP (Soin et al., 2015). The study conducted by Soin et al. (2015) used a high-frequency alternating current in an attempt to reverse cortical reorganization and found that this was an effective means to alleviate phantom limb pain, but lacked the amount of participants needed to generalize these results to a greater population. Other studies looked at deep brain stimulation and dorsal root ganglion stimulation, both of which proved to be effective in the treatment phantom limb pain. The findings of Bittar et al. (2005) and Eldabe et al. suggest that stimulation at the spinal and central level are more effective and have more positively consistent results than stimulation at the peripheral level.

Section III: Non-Pharmacological, Non-Invasive Treatment Strategies

In some cases a patient’s PLP is highly resistant to pharmacological or invasive forms of treatment. When this resistance to treatment occurs, doctors look to non-pharmacological, non-invasive, or supportive treatment strategies to reduce PLP. Forms of supportive treatment are mirror therapy, virtual visual therapy, phantom exercises, reflexology, and hypnotism. Supportive treatments aim to reduce PLP by stopping or reversing the cortical reorganization that occurs after a limb has been amputated, through primarily visual feedback. Many studies have sought to investigate the mechanisms involved in supportive treatment of PLP as well as the efficacy of supportive treatment in the reduction of PLP.

The most common form of supportive treatment is mirror therapy, in which the patient sits in a chair with a mirror placed parallel to the patient’s midline (Rothelgangel et al., 2015). The placement of the mirror eliminates the patient’s view of the amputated limb and creates the
illusion of two intact limbs that can then be used therapeutically to reduce or stop cortical reorganization (Rothelgangel et al., 2015). A case study conducted by Kim and Kim (2012) followed an above-elbow amputee whose PLP was resistant both pharmacological and invasive forms of treatment. The patient described his phantom pain as cramping pain and electric-like pain with his phantom arm rotated medially (Kim & Kim, 2012). The patient was initially on a treatment regimen that involved multiple opioid medications, but when that regimen proved to be ineffective the patient then tried various invasive treatment techniques that also proved to be ineffective in the treatment of his PLP (Kim & Kim, 2012). During both of these treatment strategies the patient reported PLP at 8-10 out of 10 on the visual analog scale (VAS) (Kim & Kim, 2012). After the patient’s PLP proved to be resistant to pharmacological and invasive forms of treatment, he practiced mirror therapy in fifteen-minute sessions, four times a week (Kim & Kim, 2012). One week into therapy the patient reported that his medially rotated phantom was back to normal and that his PLP was a 7 on the VAS and after a month the cramping was almost gone and the patient’s PLP was down to a 5 on the VAS. The patient began practicing mirror therapy at home after two months and at this point his PLP dropped to a 4 on the VAS, but the electric-like pain was never fully alleviated. From this patient researchers Kim and Kim (2012) gathered that mirror therapy is effective for certain types of PLP, specifically deep somatic pain (pressure and proprioceptive pain) as opposed to superficial pain (warmth sense and nociceptive pain). Kim and Kim (2012) assert that this could be due to the fact that deep tissues are responsible for integrating sensorimotor nerves as well as creating movements where as superficial tissues are not. While these findings do support the hypothesis that mirror therapy is effective in reducing PLP, there was only one participant in the study thus making it difficult to generalize these results to other amputees suffering from PLP.
Researchers Brodie, Whyte, and Niven (2007) sought to provide empirical data supporting claims that mirror therapy is effective in reducing PLP by conducting a randomized controlled trial to determine if viewing an image of an intact moving leg and attempting to move the phantom leg while simultaneously moving the intact leg has an effect on PLP. In order to test this hypothesis, 80 unilateral lower limb amputees were randomly placed into either the mirror group or the control group. Participants in the mirror group were asked to place their intact limb into a mirror box, to look at the mirror image of the intact limb and to align their phantom with that image, while the control group aligned their intact leg with their phantom leg to either side of the mirror while the mirror was obscured, allowing participants to view their intact limb but not its mirror image (Brodie et al., 2007). Along with testing the effects of mirror therapy on the PLP, Brodie et al. (2007) also assessed mirror therapy’s effect on Phantom Limb Sensation (PLS) and Phantom Limb Movement (PLM). PLS is the perception of non-painful sensations (heat, cold, itch) in the phantom limb, while PLM is the amputee’s ability to intentionally move all or part their phantom limb (Brodie et al., 2007). Brodie et al. (2007) found that after one session of mirror therapy, there was no difference between the mirror group and the control group in the modification of PLP, but that both groups significantly weakened phantom sensations and phantom pain. Brodie et al. (2007) also found that the mirror condition provoked more phantom movement than the control group, suggesting that it is easier for amputees to move their phantom limbs if they have an image of an intact limb to focus on, but that a fully intact image of a limb is not needed to alleviate PLP. The findings of Brodie et al. (2007) support the findings of Kim and Kim (2012), that mirror therapy can be effective in reducing PLP, but they also took the study one step further by making a differentiation between Phantom Limb Pain (PLP), Phantom Limb Sensation (PLS), and Phantom Limb Movement.
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(PLM), and by studying what effects mirror therapy may have on these phenomena. The number of participants in the study helps to provide more empirical data on the effects of mirror therapy on PLP, but the findings of the study are not definitive enough to validate mirror therapy as an effective method of treatment for PLP.

A study conducted by Mercier and Sirigu (2009) sought to further explore how training with mirror therapy, or visual virtual feedback, can alleviate PLP. They did so by using convenience sampling to recruit eight participants who were experiencing PLP as a result of complete brachial plexus avulsion causing deafferentaion and paralysis of hand or of an above-elbow amputation (Mercier & Sirigu, 2009). All participants were shown a virtual image of their missing limb performing different movements, and were then instructed to follow those movements as much as they could with their phantom limb (Mercier & Sirigu, 2009). The difficulty of the movements was set to a level just slightly above the capacity of the participant’s phantom to encourage motor improvement (Mercier & Sirigu, 2009). All participants took part in 2 treatment sessions per week for 8 weeks and they were asked to rate their pain level on a VAS immediately before and after each session as well as complete a daily pain diary reporting background pain, frequency of spasms, and duration of spasms (Mercier & Sirigu, 2009). There was no control group (Mercier & Sirigu, 2009). The results of this study support previous findings that mirror therapy, or virtual visual feedback, can be effective in reducing PLP at least in the short term. Mercier & Sirigu’s (2009) results also suggest that virtual visual therapy can reduce PLP in the long term by showing that some participants maintained a decreased intensity of PLP as far as four weeks postintervention. Mercier & Sirigu (2009) think that the fact that all participants were at least one year post-lesion could have something to do with their susceptibility to treatment, suggesting that preexisting differences between amputees could be
related to an amputee’s susceptibility to virtual visual treatment. This study does much to show that mirror therapy/virtual visual therapy is effective in the short-term alleviation of PLP and possibly in the long-term alleviation of PLP, but not in the complete elimination of PLP.

Mirror therapy has been shown to be effective in the short-term reduction of PLP, but not the elimination of PLP. Researchers Meyer, Matthes, Kusche, and Maurer (2012) sought to investigate the efficacy of imaginative resonance training (IRT) on the elimination of PLP by conducting pre-post functional magnetic resonance imaging (fMRI) to observe cortical activity. Both participants in this study were lower limb amputees with one being a mid-thigh amputation and the other being a right foot amputation (Meyer et al., 2012). IRT is an imaginative form of body-symptom oriented, self-healing in which the amputee’s imagined body part is projected by the amputee onto a non-uniform surface for the purpose of tactile differentiation (Meyer et al., 2012). The amputee then performs exercises in an attempt to provoke stimulation in the somatosensory cortex that corresponds to the imagined body part (Meyer et al., 2012). A trainer in IRT initially led participants, but they were later able to conduct it on their own (Meyer et al., 2012). At beginning of treatment, one participant was on a pain medication regimen that he was able to end by the conclusion of IRT (Meyer et al., 2012). This participant also started IRT rating his PLP at a 70 out of 100 on the VAS, which dropped to 0 at the conclusion of IRT and remained at 0 three and a half years after IRT completion (Meyer et al., 2012). The other participant reported PLP reduction just five minutes into his first session and his PLP went from a 65 to 0 out of 100 on the VAS. FMRI results from the study also suggest functional reorganization within the sensorimotor cortices of both participants, with the participants’ fMRIs post-test resembling fMRIs of intact patients (Meyer et al., 2012). This functional reorganization
correlates with the reduction of perceived pain levels (Meyer et al., 2012). The findings of Meyer et al. (2012) support the theory that IRT could be effective in reducing PLP.

Another form of supportive treatment is phantom exercise in which the amputee imagines moving his phantom limb, thus engaging the regions of sensorimotor cortex that would be engaged if the limb were still intact (Ülger, Topuz, Bayramlar, Şener, and Erbaçeci, 2009). A study conducted by Ülger, Topuz, Bayramlar, Şener, and Erbaçeci (2009), sought to investigate the efficacy phantom exercises and the mechanisms behind them. Participants were 20 amputees all who reported their PLP at 7 out of 10 at least and all participants were asked to stop taking drugs during the experiment (Ülger et al., 2009). Of the 20 participants in the study, 10 performed phantom exercises and prosthetic training while the other 10 performed just prosthetic training and general exercises, and all participants repeated their assigned exercises for 15 minutes or until their PLP disappeared (Ülger et al., 2009). All participants regardless of group experienced a reduction in PLP intensity after four weeks of treatment and all participants reported that they continued with exercises after the experiment with a continued reduction of PLP intensity (Ülger et al., 2009). While all participants experienced significantly reduced PLP intensity, the reduction in intensity for the phantom exercise group was more significant than that of the control group, with participants in the phantom exercise group reporting lower VAS scores than participants in the control group (Ülger et al., 2009). These findings suggesting that at least attempting to engage in activities that would evoke the regions of the sensorimotor cortex helps to reverse the effects of cortical reorganization (Ülger et al., 2009). Ülger et al. (2009) assert that this cortical reorganization is countered during phantom exercises because they evoke mirror neurons in the hemisphere of the brain that contralateral to the amputated limb.
Brunelli et al. (2015) sought to integrate the prominent forms of supportive treatment and investigate the efficacy of progressive muscle relaxation, mental imagery, and phantom exercise training on PLP. Brunelli et al. (2015) randomly assigned 40 participants into two parallel groups with the experimental group participating in the SantaLucia Alleviation Intervention for Phantom Amputees’ Neurorehabilitation (SAIPAN) treatment twice a week for four weeks while the participated in standard stump rehabilitation for the same amount of time. Participants taking part in the SAIPAN treatment were induced into a relaxed state using a “body scan technique,” in which participants systematically focus on different parts of their bodies including their phantom limbs (Brunelli et al., 2015). Participants then performed imagined movements with their phantom limbs that progressed to phantom exercises in where participants were required to imagine their phantom limb, then position their intact limb in the mirror opposite position of their phantom limb and then move both limbs in opposite directions and then back to their starting positions (Brunelli et al., 2015). These exercises were performed for 15 minutes or until the participant no longer felt pain in their phantom limb (Brunelli et al., 2015). Brunelli et al. (2015) found no significant difference between groups at baseline, but those that were in the experimental group and received SAIPAN treatment experienced reduced rate, duration, and intensity of PLP at the one-month follow-up. The significant findings so long after the end of the study suggest that the treatment has an after-effect or that the treatment has long lasting effects (Brunelli et al., 2015). Brunelli et al. (2015) believe that the success of their study is due to the cumulative effects of the multi-faceted treatment approach. The findings of Brunelli et al. (2015) show that the SAIPAN treatment is effective in the short-term and mid-term reduction of PLP, but for future studies it would be interesting to see if this treatment could be effective in the long-term.
Supportive treatments aim to reverse cortical treatment by stimulating affected regions of the somatosensory cortex. This can be accomplished many different ways, but it is primarily by using visual feedback or imagining visual feedback. Mirror therapy is the most well known form of supportive therapy in part due to its high level of efficacy. The case studies and experiments mentioned previously in this review further support mirror therapy and virtual visual therapy as highly effective forms of treatment for phantom limb pain. A lesser-known, yet highly effective form of supportive therapy is imaginary resonance therapy, which like mirror therapy relies on the brain’s tendency to favor visual feedback over other forms of sensory feedback in order to counteract cortical reorganization (Meyer et al., 2012). A form of supportive therapy that can be applied on its own or in tandem with the previously mentioned forms of supportive treatment is phantom exercise, which requires the amputee to engage the affected regions of the somatosensory cortex, in an attempt to keep neighboring regions from invading that cortical space (Ülger et al., 2009). Brunelli et al. (2015) in their study, which combined muscle relaxation, mental imagery, and phantom exercises, showed that these highly effective forms of treatment could also work in tandem to provide equally effective treatment of phantom limb pain.

Discussion

The findings of the studies previously mentioned suggest that forms of treatment for phantom limb pain are most effective when they directly affect the central nervous system as opposed to the peripheral nervous system. The findings of the studies previously mentioned also suggest that while progress has been made in finding pharmacological and invasive treatments that are effective in the treatment of phantom limb pain, the forms of treatment that are the most
consistent in the alleviation of phantom limb pain are supportive forms of treatment, due to their direct effect on the central nervous system.

Pharmacological treatments aim to stop cortical reorganization and dampen central sensitization by effecting mechanism at the level of the neurotransmitter. The ability to focus on specific neurotransmitters and receptors, suggests that researchers have more than an adequate understanding of how, why, and where the pain that amputees experience originates. Opioid medications may only be moderately effective in the treatment of PLP because their effects can be so widespread and unfocused in its analgesic effects, while NMDA-receptor agonists like memantine have had a marginally higher level of success due to their level of specificity. Activity at NMDA receptor sites, which mediate cortical neuroplasticity and hyperexcitability in dorsal root neurons, can be altered or affected by NMDA-receptor antagonists like memantine shortly after amputation, but have little to no effect on amputees with chronic, pre-existing PLP (Maier et al., 2003). Dual medication treatments appear to be the most effective due to their ability to counterbalance adverse effects of the medications if they were used individually. The buprenorphine/naloxone treatment studied by Licina et al. (2013) was effective because the naloxone stopped the buprenorphine’s mu agonist effects, while still providing the amputees with PLP relief.

Some disadvantages to pharmacological forms of treatment are the adverse effects that amputees can experience while taking these medications. Even when these medications are effective in reducing the intensity of PLP or of countering the effects of cortical reorganization, there are complications involving side effects or drug dependence that must be taken into account. Participants in the study conducted by Huse et al. (2001) experienced the analgesic effects of MST, but some also experienced dizziness, fatigue, and constipation at follow-ups.
after the study. These additional effects that experience after the conclusion of the study suggest that participants also did not have a gradual enough titration, which can lead to dependence (Huse et al., 2001). The amputee in the case study done by Kumar et al. (2015) could not be weaned off of oral morphine due to the fact that any time the researchers attempted to lower the dose, the amputee experienced rebound pain and opioid withdrawal. It was also suspected that the amputee was experiencing opioid-induced hyperalgesia, which is another possible side effect of opioid medications (Kumar et al., 2015). While NMDA-receptor antagonists can be moderately effective in their treatment of PLP, when the dose exceeds certain volume unpleasant side effects, such as restlessness, hallucinations, anxiety disturbances, nausea, and fatigue can be experienced (Maier et al., 2003). Another disadvantage to pharmacological forms of treatment is their ability to interfere with other medications that the amputee might be taking. This was the case with the patient in the study conducted by Spiegel et al. (2010), who was also experiencing symptoms of depression while she was taking duloxetine and pregabalin for the treatment of her PLP. The efficacy of the duloxetine/pregabalin treatment was inconclusive due to the patient’s depression.

Invasive forms of treatment are able to reduce PLP intensity and counter the effects of cortical reorganization by affecting nerves either through stimulation or through a nerve block at the peripheral, spinal, and central levels of the nervous system (Bittar et al., 2005). Stimulation at the level of the central nervous system has been effective in the fact that the affected cortical areas of interest can be directly targeted. This was the case in the study conducted by Bittar et al. (2005), where upon inserting deep brain stimulation electrodes into the contralateral periventricular gray and sensory thalamus and then connecting those leads to a subcutaneous pulse generator, participants experienced long-term PLP relief and alleviation. These findings of
PLP relief through deep brain stimulation were replicated by Pereira et al. (2013). At the spinal level was also seen has highly effective according to the findings of Eldabe et al. (2015), who implanted stimulant contacts near the dorsal root ganglions of amputees to produce an analgesic effect. Treatments that affect mechanisms in the periphery are effective on the basis that there are different ways of creating an analgesic effect. The most common way is through producing an electrical nerve block, as was done by Soin et al. (2014), or by directly stimulating the nerve affected nerve, as was done by Rauck et al. (2014). A lesser know, but still highly effective treatment that works on the peripheral mechanisms is cryoanalgesia, which creates long lasting analgesic effects by applying cold to the nerves and damaging the blood supply to the nerves (Moesker et al., 2014).

One major disadvantage to invasive forms of treatment is that they are invasive. By going into the body and physically altering one or many nerves after these same nerves have already been damaged, amputees are running the risk of doing further damage and experiencing more intense pain. Neuromas, which can occur as a result of limb amputation can cause a significant amount of pain and can reform even after being surgically removed making invasive treatments to that end ineffective. Another disadvantage is that in order for an analgesic to be produced through electrical nerve stimulation or through a nerve block, voltage, frequency, and placement must be just right, and what works for one patient cannot always be generalized to the greater population (Eldabe et al., 2015). Upkeep and maintenance can also be a setback if bandages and covers need to be kept dry or constantly changed, and leads can be pulled out accidentally (Rauck et al., 2014).

Supportive treatments are effective in their treatment of PLP due to their ability to reduce pain intensity and counter the effects of cortical reorganization by using visual feedback.
This use of visual feedback is so effective because of the brain’s tendency to favor visual stimuli over other sensory stimulation. The studies conducted by Kim and Kim (2012) and Brodie et al. (2007) showed that a fully intact image is not needed for mirror therapy to be effective, as long as the amputee has at least a distorted representation of the missing limb. Supportive treatments are also effective in their treatment of PLP due to their ability to combine both visual feedback and sensorimotor feedback to counteract the effects of cortical reorganization and the resulting pain that comes with it. The SAIPAN treatment that was used by Brunelli et al. (2015) combined mental imagery, which relies predominantly on visual feedback, and phantom exercises, which uses limb movement to stimulate the affected parts of the sensorimotor cortex, to reduce the rate, duration, and intensity of PLP both immediately after the experiment and in follow-ups. The use of supportive forms of treatment should probably a continuous process since they rely on sensory feedback to combat the effects of cortical reorganization. This continuation of supportive treatment is more reasonable than continuous use of pharmacological forms of treatment because with supportive treatments there is no risk of side effects or medicinal dependency.

A possible disadvantage to supportive forms of treatment is that they may not work on all forms of PLP. Kim and Kim (2012) found that mirror therapy was more effective in the alleviation of deep somatic pain (pressure and proprioceptive pain) than superficial pain (warmth sense and nociceptive pain), due to the fact that deep tissues are responsible for integrating sensorimotor nerves and movements whereas superficial tissues are not. Another disadvantage to at least mirror therapy and possibly other forms of motor therapy is that these treatments seem to be aimed primarily at unilateral amputees. Mirror therapy would be ineffective for a double limb amputee because a mirror image would just be another amputated limb. Supportive
treatment would also be ineffective for blind amputees on the account that visual feedback cannot be used.

While all three forms of treatment for PLP have their advantages and disadvantages, the most effective and feasible forms of treatment tend to be the ones that combine multiple approaches in an attempt to alleviate PLP. In the future maybe the most effective treatment will involve the mechanisms that the major areas that contribute to the formation of PLP: the formation of neuromas on the effected nerves, the incongruent sensory feedback that results in sensations of pain, and the cortical reorganization that occurs when neighboring areas in the sensorimotor cortex encroach on the affected area.
References


acid receptor antagonist, memantine, in patients with chronic phantom limb pain.

*International Anesthesia Research Society, 98*, 408-413.