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Phantom Limb Pain: Implications for Treatment When the Mechanisms Are Unknown

Trinity Neve

PHANTOM LIMB PAIN: IMPLICATIONS FOR TREATMENT WHEN THE MECHANISMS ARE UNKNOWN

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By

Trinity Neve

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Thesis Written By

Trinity Neve

Approved by

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Thesis Advisor

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Thesis Reader

Accepted by

____

Director, Honors Program

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Preface and Acknowledgements

When choosing a topic for my thesis, I wanted to find a subject that combined my current educational journey with my future one. In other words, I wanted to find a topic where neuroscience and physical therapy merged. While the topic of phantom limb pain has come up in some of my neuroscience classes, I really began to fall in love the with the complexity of it while reading *Phantoms in the Brain* by Ramachandran and Blakeslee (a quotation from this book can be found in Chapter 2 of my thesis). Ramachandran not only hypothesized his own theory behind phantom limb pain, but developed a physical therapy practice known as mirror therapy to help treat the disorder. This made phantom limb pain a perfect fit, as it allowed me to use my background in neuroscience to explore the mechanisms of the disorder, as well as investigate how we treat the disorder.

First, I would like to thank Dr. Ashley Fricks-Gleason, my advisor, for her support through the duration of the process. She was always there to encourage me, keep me on track, and help me improve my writing. Dr. Fricks-Gleason has continually expanded my love for neuroscience throughout my time at Regis University. Secondly, I would like Dr. Amanda Hine, my reader, for her aid in this project. I went into this process knowing very little about bioethics. Dr. Hine helped me develop my arguments as well as demonstrated to me the importance of the field.

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CHAPTER 1: PHANTOM LIMB PAIN

History

In 1536, a man named Ambroise Paré joined the French army as a surgeon. He became a leading pioneer of surgery, specifically amputation (Axoiti, Geramani, Sarbu, & Karamanou, 2014). During the mid-sixteenth century, deep gunshot wounds would lead to gangrene. Because of this, amputation was necessary. At the time, cauterizing the wound was the most widespread way to stop the bleeding, but Paré looked for more effective, less painful methods. Paré began to use ligatures, silk thread, to tie around the blood vessels to stop the bleeding. However, at the time, this process was too slow and ineffective due to the lack of antiseptics. During his time as a military surgeon, it is believed that Paré was the first to report and write about amputee soldiers that were still cognizant of their missing limb (Richardson, 2010). The first time that Paré describes the syndrome is in *The Method of Treating Wounds Made by Harquebuses and Other Guns*), Paré portrays the syndrome as well as provides multiple different models for such pain (L. Nikolajsen & Jensen, 2001). In Chapter 23 of his complete works, Paré writes, “The patients imagine they have their members yet entire, and yet doe complain thereof (which I imagine come to pass, for that, the cut nerves retire themselves towards their original, and thereby cause a pain like to convulsions)” (Paré, 1575, as cited in Finger & Hustwit, 2003, p. 677) In other words, Paré describes that the individual has a painful sensation as though their whole limb is still intact. He then continues that he believes the cut nerve is the reason for this pain. In this quote, it can be seen that Paré hypothesizes that the painful sensation (phantom limb) comes from the nerve being cut during amputation.

After Paré, others began to describe this pain in missing limbs. In 1830, Charles Bell published a monograph called *The Nervous System of the Human Body.* This monograph serves as the first descriptor of several different neurological disorders. In it, Bell describes an amputee who still has phantom limb pain and the perception of motion. Bell theorizes that the reason for this phantom limb is "muscular sense," a term that he had already coined (Furukawa, 1990). In this, Bell describes how individuals know where their muscles are without the need for touch, and this is the reason that phantom limb pain exists. Bell's understanding of muscular sense is similar to our current view of proprioception. Currently, proprioception has a similar definition in that proprioception is the ability to understand the location of our body parts in regards to other parts, including body equilibrium and balance. Magendie (1833), Rhone (1842), and Gueniot (1862) also provided detailed descriptions of phantom limb (L. Nikolajsen & Jensen, 2001).

In 1866, a Civil War surgeon named Silas Weir Mitchell published a piece in The Atlantic Monthly. The article called "The Case of George Dedlow" describes a surgeon whose training is interrupted by entering the Union Army as an infantry officer (Mitchell, 1866). During his time in the army, George Dedlow loses all four of his limbs to amputation. The story goes on to discuss a head and trunk who still feel sensations of the missing limbs. The work of Mitchell is of particular interest to scientists because of its accurate depiction of the neurological issues such as these phantom sensations (Canale, 2004). This story made a large impact on the general public because of this depiction as well as the ending in which it describes a séance in which Dedlow is reunited with his legs. At the beginning of the article, Mitchell (2004) says "I ought to add, that a good deal of what is here related is not of any scientific value whatsoever," (p. 113). Even with this statement, the article had a large impact on the public perception of amputation.

It is Silas Weir Mitchell who was the first to attribute the term "phantom" to these sensations that he describes in the "The Case of George Dedlow" (Richardson, 2010). Furthermore, Mitchell coined the term phantom limb pain, what these sensations are called now. In 1872, Mitchell discusses the phenomenon in a scientific manner in his book *Injuries of the Nerves and their Consequences.* In the chapter "Neural Maladies of Stumps," Mitchell gives case examples of the physiology of the stump and the sensory hallucinations that come with it (Mitchell, 1872). In his book he states, "Among ninety cases, including a great variety of amputations, I have found but four cases—two of an arm, the others of legs—in which there never had been delusion as to the presence of the absent member," (Mitchell, 1970, p. 348). He goes on to discuss the faradization of the stump of an arm, which produces a feeling in the hand. Faradization is the stimulation of the stump of the arm with electrical current. In his account, Mitchell is describing what we have come to know as phantom sensations. Mitchell describes the sensory impressions behind such a feeling, and as such, defines his own version of why he believes phantom limb sensation exists.

Reports on this pain continued into modern times due to amputations in World War I, World War II, the Vietnam War, and the Israeli war (Edwards, Mayhew, & Rice, 2014; Foote, Kinnon, Robbins, Pessagno, & Portner, 2015; Heszlein-Lossius et al., 2018; Machin & Williams, 1998). Continued research investigated other reasons for amputation such as peripheral vascular disease (commonly due to arteriosclerosis and neoplasms (benign or malignant growths; L. Nikolajsen & Jensen, 2001). During this time, it was believed that phantom limb pain existed in a small subset of individuals and early research showed the incidence of such pain to be around 4% (Henderson & Smyth, 1948). At this time, phantom limb pain was measured by whether a patient asked for pain medication or not, and this is most likely the reason why newer research has found a higher percentage for the incidences of pain (L. Nikolajsen & Jensen, 2001).

From Paré's time in 1536, a number of hypotheses and theories have been developed in order to explain this phantom limb pain (Finger & Hustwit, 2003). Bell used "muscular sense" to explain the pain, while Mitchell, describes it as being due to sensory impressions. Even with the identification of the disorder such a long time ago, the neurological phenomenon of phantom limb pain and the mechanisms behind it are still not fully understood (Flor, Nikolajsen, & Jensen, 2006).

Phantom Limb Prevalence and Variances

Before beginning a discussion behind the etiology of phantom limb pain, it is important to differentiate it from phantom sensations and residual limb pain (or stump pain). Phantom limb sensation is any sensation felt in the amputated limb that is not pain. Residual limb pain is any pain felt in the stump of the amputated limb (Ahmed et al., 2017). Phantom limb pain is a painful sensation in reference to the missing limb. This pain can begin as early as right after the removal of the limb, and can be described as any combination of the following descriptors: "stinging, cutting, piercing, radiating, tight, nagging, squeezing, tingling, and shocking" (Ehde et al., 2000, p. 1040). While phantom limb pain is normally thought of as pain to an amputated limb, this pain can be found from removing other parts of the body. Examples include, but are not limited to pain in removed teeth, genital organs, bladder and breasts (Woodhouse, 2005). Even though it is not uncommon for phantom limb pain to occur in these areas, most research on phantom limb pain is focused on amputated limbs.

There is a large amount of variation within phantom limb pain among individuals with amputations. Such variation can be found in the intensity and duration of the pain. For most individuals, the phantom limb pain is episodic and is not constant (Whyte & Niven, 2001). On a scale of 0 (no pain) to 10 (pain as bad as it could be), an average pain score of 5.1 was found (Ehde et al., 2000). It is important to note that the standard deviation was 2.6, showing that there is large individual variability in the intensity of the pain. Furthermore, in this same study, when looking at the duration of the pain, over half of the individuals reported their pain only lasting a few minutes (52%), while others reported periods of an hour (26%). While there is variation in the episodes of phantom limb pain, there seems to be no difference in reports of phantom limb pain in regards to if the limb is an upper or lower extremity (Poor Zamany Nejat Kermany, Modirian, Soroush, Masoumi, & Hosseini, 2008).

There are also variations in when phantom limb pain first occurs, and how outside variables can impact the incidence of it. Jensen, Krebs, Nielsen, & Rasmussen (1983) found that 47 percent of individuals had pain in the first 24 hours following amputation. This number grew to 84 percent eight days post-operation, and 90 percent after six months (T. S. Jensen et al., 1983). A study by Ehde et al. (2000) reported a slightly smaller number of 72 percent of individuals had phantom pain within six months of their amputation. That is to say that roughly half of the individuals first experience phantom limb pain within a day, but the onset can still occur up to six months following amputation. Additionally, it has been shown that environmental factors can increase the incidence of pain. Environmental factors such as pre-amputation pain, smoking after proximal level of amputation, and postoperative analgesia have all be found to increase pain levels (Ahmed et al., 2017; Yin et al., 2017). On the other hand, presurgical interventions such as perioperative epidural blockade do not seem to prevent the onset of phantom limb pain (Nikolajsen, Ilkjaer, Christensen, Krøner, & Jensen, 1997).

Theories Behind Phantom Limb Pain

Just like the variance within the pain itself, there are variations in the theories describing phantom limb pain. The neurological mechanism of phantom limb pain is still unknown. At first, theories revolving around phantom limb pain were psychological in nature, but now there is increasing evidence that the pain is neurological in nature (Flor et al., 2006; Raffin, Richard, Giraux, & Reilly, 2016; Seo et al., 2017). Three main theories have been implicated in phantom limb pain and involve the peripheral nervous system, the central nervous system, and body schema.

Peripheral nervous system.

The peripheral nervous system includes all parts of the nervous system except for the brain and spinal cord. A study done by Zeng, Wang, Guo, He, & Ni (2016) showed similar results when performing neuroma infiltrations, only the pain in the stump was reduced. They had different results when performing a nerve block. In this study, a femoral and sciatic nerve block was performed and the result was longer pain relief. There was an 80% pain reduction in both stump pain and phantom limb pain that lasted 40 hours for the subject (Zeng et al., 2016). This study was only a case report, and because of this, the effect of targeting of the femoral and sciatic nerves might be different with a larger subject pool, or the results may vary with an upper extremity.

With this being said, intravenous regional anesthesia has been noted to give rise to phantom limb pain in individuals without amputation (Dominguez, 2001; Paqueron, Lauwick, Le Guen, & Coriat, 2004). Reports have been given where the body part feels like a phantom and is stuck in one position until intravenous regional anesthesia is stopped. It should be noted, that intravenous regional anesthesia does not normally have this effect on individuals. Still, these reports show that the peripheral nervous system might have a larger effect on phantom limb pain than previously thought.

Other theories that pinpoint the peripheral nervous system as the reason behind the pain focus on spinal nerves. There are two roots leading into/out of the spinal cord, the dorsal root and the ventral root. The dorsal root is responsible for the afferent, or incoming, sensory information; whereas the ventral root is responsible for the efferent, or outgoing, motor information. In a study by Vaso et al. (2014), they suggest that phantom limb pain is caused by an increased input from afferent sensory inputs to the dorsal root ganglion. This increased sensory input is due to axotomized (cut axons of) neurons during amputation. In their study, an intraforaminal block almost completely reduced phantom limb pain in their subjects, suggesting that the dorsal root ganglion is the spontaneous generator of a phantom limb. In this study, they only blocked one root, while multiple roots innervate the leg for sensory stimulation. The exact reason for why it still provided relief is unknown, but it could be because the majority of cases with phantom limb experience the pain in the foot, and this was the root that was blocked.

Even with all of this evidence, most have abandoned peripheral nervous system theories due to the fact that phantom limb pain frequently persists despite neuroma infiltration and nerve/plexus block (Birbaumer et al., 1997). These types of treatment tend to alleviate stump pain, but not phantom limb pain. Therefore, a large proportion of phantom limb pain research has since been directed on the origin of phantom limb pain being in the central nervous system.

In summary, while research has been steering away from the peripheral nervous system for answers with regard to phantom limb pain, it seems to still have some involvement. It is now known that the involvement is not directly at the site of the neuroma but may be higher up along the peripheral nervous system. This could mean increased activity at the spinal nerves themselves (as seen by the femoral and sciatic nerve blocks) or even as high up as the dorsal roots.

Central nervous system.

The central nervous system contains the brain and the spinal cord. Phantom limb pain theories that involve the central nervous system identify maladaptive brain plasticity as the cause (Birbaumer et al., 1997; Flor et al., 2006). There are multiple locations in which this brain plasticity begins to take place. They include the primary somatosensory cortex (postcentral gyrus), the primary motor cortex (precentral gyrus), and within commissural fibers (connecting the two hemispheres of the brain).

Within the somatosensory strip, certain areas are devoted to certain body parts. This is often described as a homunculus (Snyder & Whitaker, 2013). This image depicts both the somatosensory and motor strips and shows what area of each strip is devoted to what body part. When a limb is amputated, this cortical organization begins to restructure (de Klerk, Johnson, & Southgate, 2015). When the trunk or face is stimulated on the ipsilateral side of the amputation, phantom limb sensations can be evoked (Knecht et al., 1996). The trunk and the face are the two regions that are next to the arm on the homunculus. Moreover, when assessed with MRI imaging, the cortical region for the limb is also evoked when the trunk or face is stimulated (Knecht et al., 1996). This sensation is not limited to just the ipsilateral side though, as contralateral stimulation also causes some sensation and because of this, interhemispheric structures must also be involved. Additionally, artificial stimulation can be engineered in humans (Lee et al., 2018). In a study by Lee et al. (2018), they stimulated the cortex with subdural mini-electrocorticography grids. In doing so, they were able to induce artificial somatization during a behavioral task. By varying parameters such as increased pulse width, current strength, and frequency, they increased such sensations. With this being said, the cortical structure for the area is still relatively intact and resembles closely to that of a normal cortex (Björkman et al., 2012). In the study by Bjorkman et al (2012) they demonstrate through functional magnetic resonance imaging that when the stump is stimulated the area that used to contain sensory information for the fingers is still being stimulated. This means that although there is somatosensory cortex restructuring in people with amputations, this restructuring is not complete.

These maladaptive changes can also be found in the primary motor cortex in comparing individuals with hand amputation to healthy individuals (Raffin et al., 2016). This theory proposes that due to lack of stimulation in these areas, restructuring begins to take place. In particular, this causes the primary motor cortex to reorganize itself to utilize the under-stimulated area. In the study done by Raffin et al (2016), through functional magnetic resonance imaging, they found asymmetries between hemispheres for upper limb amputees. Specifically, there was a difference in the lip and elbow areas, but not the hand representation. This means that there was cortical reorganization in the areas surrounding the hand, where the pain was felt, but no reorganization of the had area itself. Furthermore, the less control that the individual had over their phantom limb, the more restructuration had taken place. On the contrary, if the individuals felt that they could move their phantom hand, they had less topographic changes in the lip and elbow areas (Raffin et al., 2016). More topographic changes led to higher intensity of their phantom pain. This adds to the complexity of what mechanisms are forcing the cortical reorganization.

Returning to the idea that there are changes in bilateral mechanisms, it can be seen that interhemispheric interactions are also changed after amputation. It has been found that there are microstructural changes in the white matter tracts of commissural fibers connecting the premotor cortices (Jiang et al., 2015). This means that the cortical restructuring is not limited to just the side that contains information for processing the amputations (contralateral), but the opposite side as well.

To summarize, central nervous system maladaptive plasticity is one of the leading theories in regard to phantom limb pain. Changes in the connections of the brain have been seen in the somatosensory strip, the motor strip, as well as interhemispheric structures. While these theories do a good job of explaining the overall sensation, they do not discuss at what point these sensations transform into pain and what causes this change to take place.

Body schema.

A third theory implements the idea of body schema. Body schema is an internal awareness of an individual's body and the relationship between body parts. This theory relates most closely to that of the previous theory involving the central nervous system and should be regarded as an expansion on it. In this theory, there is the belief that there is no afferent signaling from the limb, but the central nervous system still believes there is based on the neurocircuitry still present (Jerath, Crawford, & Jensen, 2015). Such locations of spatial processing could include the parietal lobe. A large amount of work done on the body schema theory is theoretical, and few studies have been done proving its significance.

Relief from phantom limb pain can also implicate the body schema theory. One study describes a case in which scratching and touching another person's body or one's own prostheses was helpful in relieving pain which may provide further support for the idea of body schema and image (Weeks & Tsao, 2010). This study was only a case report, but this report implies the potential involvement of the visual system in phantom limb pain.

The rubber hand paradigm is further support for the body schema theory. In the paradigm, one believes that the touch that is applied to rubber hand is actually taking part in one's own body (Botvinick & Cohen, 1998). This is due to the simultaneous stimulation of one's own hand, while also committing visual feedback to the hand itself. The brain integrates these two events into a single event in which its own hand is being touched (Metral, Gonthier, Luyat, & Guerraz, 2017). This illusion provides support to why touching another person could relieve phantom limb pain and provides support to the body schema theory. A theory that in regards to the phantom limb is mostly theoretical.

Though body schema theory may be considered an extension of central nervous system maladaptivity, this maladaptivity does not necessarily explain how the involvement of other individual's body parts can relieve phantom limb pain.

Conclusion

All of these models are conflicting both in theory and in data. At the same time, in other places, these theories overlap with similar mechanisms and similar parts of the nervous system being described. Still to this day, no exact neurological mechanism has been found to fully explain phantom limb pain (Stockburger, Sadhir, & Omar, 2016). Further research on phantom limb pain must be done in order to discover the true reason behind it. The next chapter will examine the ways that we treat phantom limb pain, even when so little is known about its cause.

CHAPTER 2: TREATMENT OF PHANTOM LIMB PAIN

The following quotation comes from the book *Phantoms in the Brain* by Ramachandran and Blakeslee (1998). Ramachandran was the first to invent and use mirror therapy for the treatment of phantom limb pain:

> "To enable patients like Irene to perceive real movement in their nonexistent arms, we constructed a virtual reality box. The box is made by placing a vertical mirror inside a cardboard box with its lid removed. The front of the box has two holes in it, through which the patient inserts her "good hand" (say, the right one) and her phantom hand (the left one). Since the mirror is in the middle of the box, the right hand is now on the right side of the mirror and the phantom is on the left. The patient is then asked to view the reflection of her normal hand in the mirror and to move it around slightly until the reflection appears to be superimposed on the felt position of her phantom hand. She has thus created the illusion of observing two hands, when in fact she is only seeing the mirror reflection of her intact hand. If she now sends motor commands to both arms to make mirror symmetric movement as she was conducting an orchestra or clapping, she of course "sees" her phantom moving as well. Her brain receives confirming visual feedback that the phantom hand is moving correctly in response to her command" (p. 46).

As discussed in the previous chapter, the mechanisms behind phantom limb pain are poorly understood. Because of this, it makes sense then that the treatment options for phantom limb pain are just as variable in their mechanisms and effectiveness. In a survey done on American Veterans over their chronic stump and phantom pain, only 1% of participants reported a lasting relief of treatment (Sherman, Sherman, & Parker, 1984). This survey demonstrates the ongoing challenge of the treatment of phantom limb pain. This chapter will give an overview of the common treatment options for phantom limb pain such as medication, injections, and more invasive interventions such as surgery. It will then further explore the use of mirror therapy as a treatment. Mirror therapy is one effective treatment for phantom limb pain, yet the reason why is not clear. This chapter focus on its use in phantom limb pain, and potential mechanisms for why it is effective.

Treatment Options

Medications

Medications are a common treatment for phantom limb pain because they are minimally invasive and are already prescribed for many types of pain (Everdingen, Graeff, Jongen, Dijkstra, & Vissers, 2017; Moura et al., 2018). Some medications that are used to treat phantom limb pain include opioids, NMDA receptor antagonists, non-steroidal, anti-inflammatory drugs, anticonvulsants, and antidepressants (Alviar, Dungca, & Hale, 2016).

Opioids work by mimicking endogenous enkephalins and endorphins. Opioids bind onto the receptors for enkephalins and endorphins, modulating the body’s pain response. Opioids are prescribed for a variety of chronic pain disorders, and this is why they are prescribed for phantom limb pain as well. Opioids have been found to be an effective treatment for relieving phantom limb pain symptoms (Alviar et al., 2016). This effectiveness has been found for both oral and intravenous use of morphine for phantom pain treatment (Huse, Larbig, Flor, & Birbaumer, 2001; C. L. Wu et al., 2002). Pain relief when using morphine was found in up to fifty percent of patients with phantom limb pain but was found to be more effective in relief for stump pain (C. L. Wu et al., 2002). Even with the effectiveness of opioids in some individuals, common side effects of opioids include tiredness, dizziness, sweating, constipation, urination difficulties, nausea, vertigo, itching, and shortness of breath (Huse et al., 2001). Furthermore, opioid use carries a high potential for addiction. This is particularly relevant for the veteran population who have a high comorbidity of other psychiatric illnesses such as post-traumatic stress disorder (PTSD; Wilder et al., 2016).

Another medication that has had found mixed results is NMDA receptor antagonists. These drugs decrease the activity at certain receptors within the nervous system, called NMDA receptors. Normally, these receptors cause hyperalgesia, neuropathic pain, and reduced functionality of opioid receptors. In regards to a phantom limb, these medications block the NMDA receptors in the dorsal horn of the spinal cord, which are responsible for the majority of sensitization and hyperexcitability. There are different types of these NMDA receptor antagonists, each of which shows differences in effectiveness. For example, memantine has been shown to be no different than a placebo in relieving phantom limb pain (Mair et al., 2003), whereas dextromethorphan has been shown to increase pain relief up to fifty percent, and had very little side effects in the study (Abraham, Marouani, Kollender, Meller, & Weinbroum, 2002). While it has been found effective, the length of the study only showed short-term effectiveness, and additional research is needed to validate their effectiveness over a longer duration.

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly used treatment for phantom limb pain after opioids and acetaminophen (Hanley, Ehde, Campbell, Osborn, & Smith, 2006). Typically, NSAIDs work as nonselective inhibitors of the enzyme cyclooxygenase (COX) (Sukhtankar, Lee, & Rice, 2014). COX normally catalyzes the formation of prostaglandins, a neurotransmitter that transmits pain. Over 20% of respondents to a survey of those with lower limb amputations responded that if they were receiving treatment for phantom limb pain it was with NSAIDs (Hanley et al., 2006). Even with the frequency of use, little research has been done on the effectiveness of treatment of both acetaminophen and NSAIDs. In the same survey, over half of the respondents using NSAIDS ranked their effectiveness as 1 or 2 on a scale of 1-5, which represented very little relief as a result of the drug (Hanley et al., 2006). NSAIDs work by inhibiting the enzymes needed to synthesize prostaglandin, a neurotransmitter that works to increase pain. Acetaminophen has similar effectiveness reported as NSAIDs (Hanley et al., 2006). The mechanism of action of acetaminophen is not fully understood, but it is believed that it is a weak inhibitor of prostaglandins (similar to NSAIDs), with a different mechanism of action (Sharma & Mehta, 2014). Though acetaminophen and NSAIDs are commonly prescribed, there is little research other than self-report data on how effective they are on relieving phantom limb pain.

Both anticonvulsants and antidepressants are medications that are normally used to treat other disorders, seizures, and depression, respectively (Margolis, Chu, Want, Copher, & Cavazos, 2014; Thase & Schwartz, 2015). Anticonvulsants increase the activity of inhibitory neurotransmitters and therefore decrease the overall activity of the central nervous system. By doing so, it is thought they can reduce pain, which is normally transmitted through excitatory mechanisms, such as by the neurotransmitter glutamate. Antidepressants typically increase the concentration of different neurotransmitters, such as serotonin, within the central nervous system. While both of these medications are sometimes prescribed for phantom limb pain, there is conflicting research supporting their effectiveness. One study on the use of gabapentin (anticonvulsant) found the drug effective in decreasing phantom limb pain intensity, while another found no difference between gabapentin and a placebo (Bone, Critchley, & Buggy, 2002; D. G. Smith et al., 2005). Due to the paucity of research on these types of drugs with respect to phantom limb pain, it is difficult to support their use in the treatment of phantom limb pain. In particular, these types of drugs may only be effective in a small group of individuals.

As outlined above, there are mixed results on how effective medications are in treating phantom limb pain. It has been found that there is not one medication that effectively relieves pain for all patients. Additionally, it should be noted that these medications are not curing the basis of phantom limb pain, but only treating the symptoms with varying degrees of success. These medications have a large number of adverse side effects, and as such, they should only be used on a patient by patient basis.

Noninvasive treatment

Noninvasive treatment options for phantom limb pain include nerve stimulation, acupuncture, and mirror therapy (Mulvey et al., 2010; Trevelyan, Turner, Summerfield-Mann, & Robinson, 2016; Young Kim & Young Kim, 2012). Mirror therapy will be discussed in depth later in this chapter.

Transcutaneous electrical nerve stimulation (TENS) is a tool for pain management that provides short-term relief for people with chronic pain. There are minor side effects as compared to other treatments of phantom limb pain such as pharmacological interventions. TENS units work to excite/stimulate sensory nerves through an electrical current. In doing so, the unit activates natural pain relief mechanisms. It is believed that the TENS units target two naturally occurring systems: the pain gate mechanism, and the endogenous opioid system. The relationship between frequency and intensity of the stimulation and the systems it interacts with, as well as its optimal pain-relieving properties, is unclear (Köke et al., 2004). TENS has been found to be an effective treatment of stump pain (Mulvey et al., 2010). In this same study, it was shown that appropriate electrode placement could evoke TENS sensations in the phantom limb, which relieved the pain of phantom limb (Mulvey et al., 2010). Additionally, research has shown TENS to be an effective pain management tool for those with phantom limb pain (Tilak et al., 2016). It should be noted, however, that the use of TENS does not provide long-lasting effects on the pain.

It is believed that acupuncture has a similar mechanism of action as TENS in that it activates the endogenous opioid system in order to provide pain relief (Housley, 2016). Acupuncture involves inserting very thin needles into the skin at strategic points around the body. The research done on acupuncture and its effects on phantom limb pain are small, coming mostly from case studies and trials. In one such small trial, acupuncture was shown to be effective in relieving the maximum intensity of phantom limb pain as well as average pain intensity (Trevelyan et al., 2016). Some participants received acupuncture in the affected limb, some received it in the contralateral limb, and some received it in both. While such results are exciting, it is clear that further research needs to be done in order to determine if acupuncture is effective in treating phantom limb pain, and which location among these works the best.

Noninvasive treatments are a promising area of investigation in the treatment of phantom limb pain and will be explored further later in this chapter. With this being said, there is a lack of knowledge on the exact mechanism of action of these treatments in chronic pain, and particularly in, phantom limb pain.

Minimally invasive treatment

Minimally invasive treatment options for phantom limb pain consist of spinal cord stimulation and injections. In a spinal cord stimulation, through surgery, a spinal cord stimulator is placed under the skin and a wire sends a mild electrical current to the spinal cord (Eldabe et al., 2015). The electrodes are placed in the dorsal epidural space. This is the space above the dura of the spinal cord and below the bone of the vertebrae.

When the device is turned on, it stimulates the fibers around the area of the spinal cord that is responsible for where the pain is felt. While the mechanism of action of spinal cord stimulation is not known, it is proposed to do with either altering the chemical transmission of the dorsal root of the spinal cord, or through the activation of dorsal column nuclei (Smits, Van Kleef, Holsheimer, & Joosten, 2013). When looking at phantom limb pain, spinal cord stimulation has mixed results (McAuley, Van Gröningen, & Green, 2013; Viswanathan, Phan, & Burton, 2010). While patients received the initial benefit of pain relief from the insertion of the device, one year and two years following the insertion the relief was not as strong (McAuley et al., 2013). Side effects found in phantom limb patients with the insertion of the spinal cord stimulator included allergic dermatitis to the generator and surgical site infection (Viswanathan et al., 2010). Both of these studies were conducted with small sample sizes, and because of this further research is needed in order to understand if this treatment should be prescribed to patients experiencing phantom limb pain.

Injections for phantom limb pain work on both the musculoskeletal system and the peripheral system. Examples of relief include bupivacaine and lidocaine injections which are called nerve blocks. These nerve blocks work by blocking the pain signaling of the nerves that innervated the limb. When looking at bupivacaine injections, a small study showed relief in phantom limb pain in six out of eight patients (Casale, Damiani, & Rosati, 2009). Because this was a small study, further research must be done to determine bupivacaine's effectiveness. The effectiveness of lidocaine on phantom limb pain has been examined in injections that also contained Depo-Medrol. Depo-Medrol (methylprednisolone acetate) is a steroid that works on the musculoskeletal system in order to relieve inflammation. This study also examined how injections of botulinum toxin type A could be used to treat phantom limb pain. In this study, it was found that botulinum toxin type A and lidocaine/Depo-Medrol had nearly equal relief of residual limb pain (stump pain), but did not work on phantom limb pain (Wu, Sultana, Taylor, & Szabo, 2012). While these injections are used in an attempt to target phantom limb pain, it seems they have better effectiveness in the relief of stump pain.

Minimally invasive treatments have mixed results in the treatment of phantom limb pain. Both spinal cord stimulation and injections can be seen as an effective treatment for relieving stump pain after amputation. They do not, however, seem to be effective in the treatment of phantom limb pain. Even though studies done on this subtype of treatment are all small studies, their results do not show much promise as a treatment.

Invasive treatment

Invasive treatment for phantom limb pain includes deep brain stimulation and stump revision. These surgeries are intensive and can potentially lead to a large number of side effects.

Stump revision therapy is normally done to facilitate the fitting of a prosthesis and/or treatment of a neuroma (Tintle, Baechler, Nanos, Forsberg, & Potter, 2012). Stump revision for a prosthesis can be due to skin scarring, the shape of the bone(s), or chronic ulcers that inhibit the prosthesis from fitting correctly. On the other hand, a neuroma is a benign growth of nervous system tissue which occurs after irritation or injury (amputation in this case). Neuromas typically cause a painful sensation wherever they are located. While neuromas are painful, they are not the only source of stump pain, and phantom limb pain can exist with or without a neuroma (Zeng et al., 2016). Normally, stump revision is not carried out just for the treatment of phantom limb pain. The success rate for stump revision is very high when there is a known cause for the pain (normally stump pain), but on the flip side is very low when there is no known cause and for this reason it is not typically performed only for phantom limb pain (Tintle et al., 2012). With any surgery, there is the risk of complication such as infection. For these reasons, there is very little research on stump revision's effect on phantom limb pain.

Deep brain stimulation involves the placement of electrodes deep within the brain. These electrodes provide an electrical stimulus to certain areas of the brain and either regulate abnormal activity (similar to a pacemaker) or are targeting certain cells to trigger the release of specific neurotransmitters (Farrell, Green, & Aziz, 2018). Deep brain stimulation is used to treat neurological disorders such as Parkinson's disease, Tourette syndrome, and chronic pain (Daneshzand, Faezipour, & Barkana, 2018; Farrell et al., 2018; Smeets et al., 2018). In the treatment of chronic pain, deep brain stimulation is successful in cases where other treatments such as medications and other more conservative measures have proved unsuccessful (Falowski, 2015). When looking at phantom limb pain, in particular, deep brain stimulation in the periventricular grey matter and the somatosensory thalamus has shown up to a 60% reduction of the pain (Abreu et al., 2017; Bittar, Otero, Carter, & Aziz, 2005). As with most phantom limb pain treatments, these studies have small population sizes, and so further research needs to be done. With this being said, deep brain stimulation effectiveness in overall chronic pain and in these small phantom limb studies demonstrates its promise.

As discussed, an invasive technique comes with more associated risk compared to more conservative measures. While stump revision surgery does not seem effective in the relief of phantom limb pain (but effective for residual stump pain), deep brain stimulation could be considered as a promising treatment. Especially in cases where more conservative treatment has proved unsuccessful.

Mirror Therapy

Much of the research on the treatment options for phantom limb pain discussed above was conducted with small sample sizes. Additionally, many of these options had adverse side effects. For this reason, the remainder of this chapter will discuss mirror therapy, which was introduced earlier in this chapter. Mirror therapy is a non-invasive treatment option, with very few side effects, that has shown promise in alleviating phantom limb pain.

Description

In the 1990s, Vilayanur S. Ramachandran invented mirror box therapy, also known as mirror therapy or virtual reality box therapy. At the beginning of this chapter, the reader was introduced to the details of Ramachandran's mirror therapy protocol. Mirror therapy can be used for both upper and lower limb amputations. Ramachandran's account was that of an upper limb amputation. In an upper limb amputation, the patient places their affected limb on one side of the box, hidden, while their healthy arm is placed on the other side. The patient views their healthy arm in a mirror. The patient is then instructed to move both arms in a symmetrical pattern. The patient views their "phantom" limb moving by looking at the mirror. The thought is that the brain is perceiving this mirrored image as the movement of the affected limb, and therefore, it reduces the pain eliminating what Ramachandran called "learned paralysis" (Ramachandran & Blakeslee, 1998). Generally, with a lower limb amputation, the same methods are performed, except a body length mirror and not a box is utilized.

The utility of mirror therapy is not limited to individuals with phantom limb pain and it has been found to have other uses in stroke and Parkinson's patients (Bonassi et al., 2016; Pérez-Cruzado, Merchán-Baeza, González-Sánchez, & Cuesta-Vargas, 2017). In these disorders, mirror therapy is employed for improvement in movement as well as a decrease in pain. Mirror therapy has been found to increase the motor recovery and motor function of upper and lower limb patients affected by stroke (Broderick et al., 2018; Pérez-Cruzado et al., 2017). Mirror therapy also increases the speed with which individuals move their limbs in Parkinson's disease (Bonassi et al., 2016).

In addition to improvement in motor recovery, mirror therapy can improve pain in their affected limbs. Following a stroke, individuals can develop complex regional pain disorder in their affected limb. In this disorder, individuals experience a throbbing or burning pain in the affected limb as well as a decreased pain tolerance in this limb. Mirror therapy provides an analgesic relief for patients with complex regional pain disorder. It reduces the pain that individuals experience in their affected limb in both intensity and duration (Cacchio, De Blasis, De Blasis, Santilli, & Spacca, 2009). These uses of mirror therapy reveal that is a promising technique for use in many neurological disorders.

Effectiveness of Mirror Therapy

Mirror therapy has been shown to be an effective way to relieve phantom limb pain (Timms & Carus, 2015). Mirror therapy has been shown to reduce the pain intensity and duration of the pain (Dall et al., 2015; Foell, Bekrater-Bodmann, Diers, & Flor, 2014). In contrast to some of the treatments outlined earlier, the pain relief was shown to extend through the duration of the treatment (Foell et al., 2014). Multiple external variables can affect the success of the treatment; for instance, it seems that treatment is the most successful for individuals who are not using a prosthesis (Barbin, Seetha, Casillas, Paysant, & Pérennou, 2016). Additionally, it appears that the treatment is the most successful for individuals who are relieving pain caused by distortional views of their phantom limb (Barbin et al., 2016). A distortional view of the phantom limb means that the patient feels as if their limb is twisted in an unnatural manner such as backwards or warped. It should be noted that mirror therapy does have some side effects, such as a vague sense of psychological irritation and confusion (Casale et al., 2009),

It should be noted that there has been some critique of the treatment of phantom limb pain with mirror therapy. While individual studies have demonstrated effectiveness, as discussed above, review papers point to heterogeneous methods and nonsignificant relief of pain (Barbin et al., 2016; Timms & Carus, 2015). These studies discuss that there are no standardized protocols (such as intensity, length, and duration of treatment) being studied in relation to mirror therapy, and because of this, its effectiveness cannot be effectively evaluated. Additionally, the treatment is critiqued due to lack of lasting pain relief. The relief normally subsides after the treatment concludes (Timms & Carus, 2015). With this being said, this treatment could be relatively simple for an individual to continue to perform on their own, in comparison to some of the invasive and pharmacological treatments discussed earlier.

Another aspect of mirror therapy that needs to be investigated further is agency. Agency may further explain the discrepancies in treatment pinpointed by the review papers. Mirror therapy seems to increase the agency that the individual has over their missing limb and the pain in most cases of treatment (Imaizumi, Asai, & Koyama, 2017). This increase is most likely due to the congruence of the predicted movement pattern, and actual sensory feedback that agreed with this prediction. Individuals who feel that they have control over their affected limb have higher rates of pain relief. This sense of agency may be a future direction in explaining the incongruence between why mirror therapy works for some, but not all individuals experiencing phantom limb pain. Another area of investigation ought to be whether there are extrinsic ways to improve agency in individuals, or if this is an intrinsic characteristic of the individual.

While it seems that mirror therapy can be an effective mechanism of pain relief for individuals with phantom limb pain, it does have some side effects. These side effects are relatively minor compared to other types of treatment discussed in this chapter. Furthermore, there needs to be more research on what type of protocol works when it comes to mirror therapy. With all this being said, the effectiveness of treatment should be looked at on a patient by patient (or case by case) basis.

Mechanisms

Like many treatments of phantom limb pain, the mechanisms of mirror therapy are unclear. One of the main mechanisms that has been proposed for mirror therapy involves mirror neurons. A mirror neuron is a neuron that fires both when an animal performs an action and when the animal sees another perform the same action. These motor neurons were first discovered in the ventral premotor cortex (F5) of the macaque monkey (Rizzolatti & Craighero, 2004). Some other areas in which mirror neurons have since been found are the dorsal premotor cortex, parietal cortex, and the primary motor cortex (Lee et al., 2018). These locations are anatomically connected to the premotor cortex. As such, it can be seen that the main role of mirror neurons is thought to be the planning and execution of movement after it has been seen. As such, it has been hypothesized that mirror neurons have to do with associative learning and it should be noted that mirror neurons are most likely also involved in somatosensation due to their existence in the parietal lobe.

In mirror therapy, it is thought that mirror neurons are triggered when the individual sees the reflection of their limb in the mirror (Finn et al., 2017; Timms & Carus, 2015). Because of this, the individual then feels the same sensation as if they were actually moving the limb. The individual does not receive any input from touch receptors telling them otherwise, as they do not exist. Mirror neurons would then modulate the somatosensory inputs being received by the brain, and, for this reason, eventually decrease the level of phantom limb pain that the individual perceives.

There are some problems with the implications of the involvement of mirror neurons in mirror therapy. This is due to the fact that mirror neurons are normally thought to be involved in goal-oriented behavior that involves the hand and/or facial expression. Specifically, they are thought to be involved in associative learning with these expressions or movements. These functions do not explain, however, how they would be involved in movements of other limbs such as the lower limbs, which mirror therapy also works on. Such conclusions are also due to the fact that most research done on mirror neurons involve these actions (Ferrari, Gerbella, Coudé, & Rozzi, 2017). Because of this, further research needs to be done to elucidate whether they are activated with the movement of other extremities.

Due to the fact that the mirror neuron system is not fully understood, and recently discovered, it is difficult to understand the system's full role in mirror therapy.

New Technology

Dr. Ramachandran himself discusses that when he invented the treatment technique, he could imagine virtual reality systems. In his book *Phantoms in the Brain: Probing the Mysteries of the Human Mind* he states, "I thought about virtual reality. Maybe we could create the visual illusion that the arm was restored and obeying her commands. But that technology, costing over half a million dollars, would exhaust my entire research budget with one purchase," (Ramachandran,1998, p. 46). Recently, virtual reality systems have come to the forefront of the research being done to treat phantom limb pain.

Typically, in a virtual reality set-up, individuals wear a head-mounted display. Through this display, individuals are shown a mirror-reversed computer graphic image of an intact arm. This means that they “see” their phantom limb when they look down. Similar to mirror therapy, individuals are asked to move both their arms in a similar movement pattern, such as a circle. In a study of eight patients, virtual reality significantly decreased individuals pain scores (Osumi et al., 2017). Furthermore, a different study applied tactile stimulation to the same side cheek as the phantom limb, the intact limb, and a no stimulation control group. Individuals were asked to “touch” objects that appeared in the virtual reality display. Stimulation was applied through vibration, similar to that found on a mobile phone. They found that the group where stimulation was applied to the cheek had the largest reduction in pain compared to the other two groups, but there was a reduction of pain in all three groups (Ichinose et al., 2017). As described in Chapter 1, the face and arm areas are near each on the sensory and motor homunculus, which may help explain why facial stimulation could enhance pain relief (Snyder & Whitaker, 2013). Via central nervous system plasticity, the areas previously devoted to the arm may have been encroached upon by the areas devoted to the face, potentially explaining how cheek stimulation would increase the analgesic effect.

Even with this said, there is isn’t enough research on virtual reality to justify the investment over mirror therapy at this point. The research on virtual reality systems has been on a small study or case study basis. While virtual reality could be a promising area in the future, at the current time there is not enough research to justify its use.

Conclusion

This chapter shows that there is a wide range of treatments available for phantom limb pain, yet none are effective for everyone with the disorder. The majority of this chapter was spent discussing mirror therapy and its potential mechanisms due to the fact that it is the only treatment for which use was developed originally for phantom limb pain (Ramachandran & Blakeslee, 1998). For this reason, mirror therapy can be utilized as a way to further investigate the potential sources of phantom limb pain. Looking forward, the next chapter will examine the treatments of phantom limb pain described in this chapter through a bioethical lens.

CHAPTER 3: BIOMEDICAL ETHICS OF TREATMENT

As discussed in the previous chapters, the treatment of phantom limb pain is very difficult. Not only are the mechanisms behind phantom limb pain not well understood, but there is no form of treatment that is effective for everyone. As such, the implications of treating this disorder must be discussed. This chapter will begin with an overview of common ethical principles that will guide the discussion of the treatment of phantom limb pain. The chapter will then outline a framework to guide clinicians through the treatments of phantom limb pain based on the one provided by Largent (2009) in the article, "Going off-label without venturing off-course: evidence and ethical off-label prescribing" to examine the ethicality of phantom limb pain treatments.

Biomedical Ethics Overview

While there are many approaches to biomedical ethics, this chapter will focus on a dominant approach which centers around four main principles. This approach is called the common morality principlism and is an effort to resolve issues that arise in clinical practice. *Principles of Biomedical Ethics by Tom Beauchamp and James Childress (2009)* explores these directing principles and their implications. The directing principles are as follows: principle of respect for autonomy, principle of nonmaleficence, principle of beneficence, and principle of justice (Beauchamp & Childress, 2009). While Beauchamp and Childress maintain that these principles are not absolutes, they can be weighed and balanced in order to create guidelines in clinical decision makings.

Moreover, these principles are not ranked in any way, but instead, need to be utilized differently depending on the clinical situation.

Principle of respect for autonomy

Autonomy is generally thought of as a state of self-governance by a group of people or institution (Autonomy, 2019). The respect for autonomy can be applied to individuals. Generally, patients should be thought of as independent beings who have the ability to make their own decisions so long as they are sufficiently autonomous. Autonomy is arguably the moral basis behind informed consent (Stoljar, 2011). The elements of informed consent are as follows: (1) the patient must have decision-making capacity, (2) the patient must receive full disclosure of the treatment, (3) the patient should understand the treatment, (4) the act must be voluntary, and (5) patient consent must be obtained (Beauchamp & Childress, 2009).

The principle of autonomy is deeply interwoven with the practice of informed consent. Informed consent allows practitioners to protect the autonomy of their patients as well as those who are not autonomous. Individuals must have decision-making capacity in order to make reasonable treatment options (directed by a physician) for themselves. If the conditions outlined above are not met, the patient cannot consent to their treatment.

Principle of nonmaleficence

The principle of nonmaleficence is based on the idea of the Hippocratic oath which states “do no harm” (Boodt, 2004). In other words, Beauchamp and Childress

(2009) define this principle as “one ought not to inflict evil or harm” (p. 151). Within a health care setting, the health care provider has an obligation to refrain from doing any unjustified harm to the patient. This is known as the harm-benefit ratio. Sometimes, harm can be associated with the treatment. Practitioners need to have the ability to balance many moral considerations in order to effectively treat a patient (Beauchamp & Childress, 2009). Sometimes, the patient and the family of this patient may see the benefits and risks differently than the practitioner, and for this reason, they need to be able to see all individuals’ viewpoints.

Principle of beneficence

The principle of beneficence requires that health care providers should promote good (Beauchamp & Childress, 2009). It refers to the actions that a health care provider does in order to benefit their patients. One way that beneficence can be demonstrated is through advocacy for protecting and defending patient’s rights. Practitioners should act in a way that promotes safety and quality of life for their patients (Chiovitti, 2011). Furthermore, this principle demonstrates the idea that the health care provider should not deprive the individual of their harmless pleasures in life. While physicians are not required to aid these individuals in such pleasures, helping them does fall under the principle of beneficence (Beauchamp & Childress, 2009).

Principle of justice

In Beauchamp and Childress (2009) *Principles of Biomedical Ethics*, the authors do not settle on one definition of justice. They choose to look at justice through multiple different theories including utilitarian, libertarian, communitarian, and egalitarian views of justice. Through examining these theories, they show that no single definition or theory can sufficiently explore medical policy (Beauchamp & Childress, 2009). While the previous three principles are more specific to the individual, this principle provides insight into the treatment of multiple individuals with similar illnesses, the entire caseload of one provider, or health policy at a national and global level (Kiddell-Monroe, 2014).

Summary

The common morality principlism remains the dominant approach in looking at clinical practice issues. The four directing principles that Beauchamp and Childress (2009) developed are the principle of respect for autonomy, the principle of nonmaleficence, the principle of beneficence, and the principle of justice. These four principles will guide this chapter's discussion of the treatment for phantom limb pain.

The Problem of Pain Treatment

Over the last two decades, chronic pain has been recognized as a public health concern by both people in the medical field as well as the general public (Bostrom, 1997; Jacox, Carr, & Payne, 1994). Experts are even going so far as to say that the treatment of pain should be considered a global health priority (Goldberg & McGee, 2011). Severe and chronic pain is very common. In one study, nearly half of the respondents reported that they had experienced severe pain at one point in their life (Bostrom, 1997). The treatment of all types of pain remains difficult due to the subjective nature of pain (M. P. Jensen, Karoly, & Braver, 1986).

Even though pain is so common, most of the pain management research studies, and resulting guidelines, have been for the treatment of cancer pain (Jacox et al., 1994; Sullivan & Ferrell, 2005). The most common approach to cancer pain is to increase dosages and different types of medications until pain relief is expressed by the patient (Jacox et al., 1994). A guideline such as this does not apply to other sources of chronic pain; conditions as common as lower back pain, or as rare as phantom limb pain. It is not practical, or safe, for individuals to be on high doses of medications that could impair their cognitive performance or impact organs for long periods of time (Salvo et al., 2011; Sukhtankar et al., 2014).

To further demonstrate the problem of pain treatment, the clinicopathological model of pain should be discussed. In such a model, the physician believes that the subjective pain an individual is experiencing is due to an objective lesion (Sullivan, 1998). As such, physicians seek out a lesion or disease to explain the pain the patient is experiencing. Many times, chronic pain does not have an objective cause that physicians can accurately point to and measure. For instance, imaging may not display a direct cause to lower back pain that improvements can be quantified from. Because of this lack of ability to find an objective source of pain, the patient and the physician are both left feeling unsatisfied about the treatment (Sullivan, 1998). Even when there is an objective cause for pain, there are still problems with pain treatment. In cancer-related pain, a lack of pain relief was found when there was a discrepancy between the physician's and the patient's estimate of the severity of the patient's pain and its interference with daily activities (Cleeland et al., 1994). This demonstrates that all types of chronic pain are subject to inconsistencies during treatment.

Another problem with pain treatment is the scales that are used to evaluate a patient's pain. Three common scales are the Visual Analogue Scale, the Verbal Rating Scale and the Numerical Rating Scale (Williamson & Hoggart, 2005). Each of these scales asks patients to rate their level of pain as indicated by a mix of verbal and numeric descriptors. While these scales provide an easy way to assess the pain of the patient, it is hard for the physician to interpret the scales (Williamson & Hoggart, 2005). These scales are valid constructs to measure pain, but they do not show the whole picture. These scales only provide information on the intensity of the pain, not the nature of the pain, or how it is directly impacting the patient's life. Additionally, the measurement of pain is individualized. For example, one patient's four on the numerical rating scale could be another person's seven on this same scale. For these reasons, sometimes the best measurement of pain is a belief in the patient (McCaffery & Beebe, 1989).

Making pain treatment even more complex, a large amount of a patient's relationship to their pain is subjective. Not only does the perceived pain vary from person to person, as discussed earlier, but the intensity can also be altered due to perceived damage that the pain might cause to the individual (Arntz & Claassens, 2004). This means that if the individual believes the pain is associated with tissue damage (such as in cancer) they tend to perceive and rate the intensity of the pain higher (Arntz & Claassens, 2004). Additionally, the intensity of a patient's pain can change due to the meaning of the pain to the individual (Arntz & Claassens, 2004). Meaning can be altered by the emotions that the individual has toward the pain such as with traumatic events associated with the pain (Ravn, Vaegter, Cardel, & Andersen, 2018). To make things even more complex, with most chronic pain, there is a high comorbidity of depression and other mental illness (Benjamin, Barnes, Berger, Clarke, & Jeacock, 1988). Such comorbidity with mental illnesses, such as depression, is thought to be due to neurobiological components shared between the two, such as a reduced level of serotonin (Boakye et al., 2016). The way that the individual perceives pain can be influenced by their mental health, as well as how the pain is presented to them.

When we turn to look at phantom limb pain, it can be seen why the measurement and treatment of this pain is so difficult. First, there is no physical evidence of the pain when the cause is phantom limb pain. These patients have an objective lesion when looking at their amputation, but this lesion only explains stump pain. Second, as discussed in Chapter 1, the mechanisms behind this pain are not understood (L. Nikolajsen & Jensen, 2001; Richardson, 2010; Stockburger et al., 2016). Third, many of the patients that experience phantom limb have had traumatic events that may lead to alterations in the way they view their pain (Cavanagh, Shin, Karamouz, & Rauch, 2006; Desmond & MacLachlan, 2006). Fourth, just as with other types of pain, there does not seem to be an objective measurement for the phantom limb pain.

Phantom limb pain is just a small subset of the pain disorders that need to be discussed, but it will remain the focus of this chapter. Choosing the correct treatment for phantom limb pain is difficult for physicians, as no one treatment exists to cure the pain.

For this reason, this chapter will provide a framework modified from “Going off-label without venturing off-course: evidence and ethical off-label prescribing” by Emily Largent (2009) in order to weigh the risk and benefits of the common treatments described in the previous chapter to better help clinicians evaluate different treatments for phantom limb pain.

Biomedical Ethics in Phantom Limb Pain

Framework Provided in “Going off-label without venturing off-course: evidence and ethical off-label prescribing” by Largent (2009)

In Largent’s (2009) article, she examines how clinicians should prescribe off-label drugs. Largent (2009) creates these guidelines because there is “very little guidance to distinguish clearly between off-label uses that are well supported by evidence and those that are not,” (p. 1745). An on-label use of a drug is the utilization of a drug for its FDA approved purpose (Aronson & Ferner, 2017). Off-label use is one in which the drug is not being used for its approved labeling use (Largent, 2009). While the off-label drug has already obtained FDA approval, it is being used outside of its approved use. For example, this would be a drug that is approved to treat breast cancer (on-label use) but is used by a physician to treat lung cancer (off-label use). Off-label drugs present a number of practical and ethical issues for physicians because they are often used with a very limited amount of information about their efficacy in the conditions for which they have not been approved. Practically speaking, strict clinical guidelines are given for a drug when it is being used on-label. For example, in on-label use, side effects can be easily identified and discussed with the patient. On the contrary, when a drug is being used off-label, new adverse side effects may arise when being used in a new disorder. Further ethical issues come forth with off-label use because clinicians must decide how much information to disclose to their patient about off-label uses. For these reasons, Largent (2009) develops a framework in order to aid physicians in the clinical decision-making process when using off-label drugs.

Signals for scrutiny.

There are four categories that the article presents in order to signify more rigorous scrutiny of the off-label use which include (1) New Drugs, (2) Novel Off-Label Use, (3) Drugs with Known Serious Adverse Effects, and (4) High-Cost Drugs (Largent, 2009). These characteristics are outlined in more detail below:

(1) New Drugs: These are drugs that have been approved by the FDA, but have been on the market fewer than 3-5 years. Drugs such as this have few clinical trials and high-quality studies proving if they work. Additionally, it is only after many years on the market that all the adverse side effects are seen, especially those that result from the long-term use of a drug.

(2) Novel Off-label Use: This is a new or unusual use for an FDA approved drug. This is dissimilar to the cancer example provided above because in that example the drug was being used for similar treatment, another form of cancer. Novel off-label use refers to a new use of the drug that might be on its own, or in combination with others, in which unknown side effects are likely to arise. For example, a drug in this category may have

been FDA approved for high blood pressure, but is being used off-label for an unrelated condition such as multiple sclerosis.

(3) Drugs with Known Serious Adverse Effects: These drugs need to be strictly monitored because they have a large risk of serious adverse side effects. While these drugs might be justified, dependent on the disorder, most of the time their risk outweighs their benefit.

(4) High-Cost Drugs: These drugs are expensive in terms of monetary value. While they might be highly effective in off-label use, they would be costly to the patient.

These signals of scrutiny should be used in order to demonstrate that the off-label prescription of these drugs needs further investigation.

Evidentiary categories.

Further investigation of these drugs should be done by examining the evidence of their net benefit. Largent (2009) outlines evidentiary categories and the recommendation for prescription provided in the chart below:

Table 1

Therapeutic Consent Recommendation based on Evidentiary Category

Category	Evidence	Recommendation
Supported	Moderate-high level of certainty of net health benefit	Routine therapeutic consent
Suppositional	Low level of certainty of net health benefit	Augmented therapeutic consent
Investigational	Very low level of certainty of net health benefit	Clinical trial/research only

Supported.

In this category, there is evidence from high-quality studies that the drug will have an increase in net health benefit. In other words, there is a large number of potential benefits as compared to potential harms. The potential harms and benefits of these drugs are supported by high-quality studies. For example, within these studies, there is a large number of participants and randomized control (Sawaya, Guirguis-Blake, LeFevre, Harris, & Petitti, 2007). Largent (2009) recommends that routine therapeutic consent be done when prescribing this drug. In other words, the consent process should be treated as if it was of on-label use. The processes of informed consent that were discussed at the beginning of this chapter should be followed.

Suppositional.

This category has a low level of certainty of net benefit. This could be because of a higher potential for harm than benefit from the drug. It could also be because the drug's efficiency is not well supported by high-quality studies. Suppositional evidence requires what Largent calls augmented therapeutic consent (2009). While the components of informed consent remain, there should be more disclosure than commonly provided when prescribing an on-label drug. Furthermore, the physician should communicate the uncertainties in terms of both potential risks and potential benefits. This type of disclosure should allow more room for the patients' beliefs.

***Investigational*.**

In this category, there is a very low certainty of net benefit. This means there is high risk associated with the drug, with low benefit, as well as very little evidence to support its use. In other words, a physician should prescribe this drug under research protocols only. She argues that these drugs require the formality of written informed consent (Largent, 2009).

Framework for Phantom Limb Pain

Largent's framework provides a place to start when discussing the treatment of phantom limb pain. While Largent's framework is dealing with off-label drug use, I argue that her framework can be helpful for the treatment phantom limb pain because none of the treatments for phantom limb pain are FDA approved specifically for use in the phantom limb. Furthermore, currently, there is limited research and evidence that support these treatments' use in phantom limb pain. The evidentiary categories that she provides will be the focus in the discussion of the treatment of phantom limb pain, as each of the treatments discussed in chapter two will be placed in one of the categories. With this being said, there are cases when the signals for scrutiny will also find their way into the discussion.

The first change that will be made is no longer will the discussion be limited to that of off-label drug use. Instead, this discussion will be expanded to all treatments available for phantom limb pain. Treatments, just like drugs, have potential benefits as well as potential harms associated with them. All treatments available for phantom limb pain are off-label use because none of them are FDA approved. Moreover, these treatments were not originally designed for the treatment of phantom limb pain (with the exception of mirror therapy), but for other forms of chronic pain (such as with opioids) or other disorders that do not involve pain (such as antidepressants).

Another change that will be made from Largent's evidentiary categories is the expansion of the suppositional category. As the discussion progresses, it will be argued that the majority of phantom limb treatments fall into this category due to the low level of support present for the treatments. The following chart below will be used to evaluate these treatments:

Table 2

Order of Use in Suppositional Category Based on Cost and Risk

Level of Risk	Level of Cost	Order of Use
Low Risk	Low Cost	1st Line
Low Risk	High Cost	2nd Line
High Risk	Low Cost	3rd Line
High Risk	High Cost	4th Line

In what follows, I will present a clinical tool for practitioners to help them navigate these treatment options with their patients. The order of use is the order in which the treatment options should be presented to their patients. The first line are those treatments that should be prescribed and tried first, the second line should be prescribed second and so on. The categories of risk and cost are chosen to further evaluate these treatments due to the bioethical principles discussed at the beginning of this chapter. I argue that risk needs to be evaluated due to the principle of nonmaleficence. Physicians should be prescribing drugs first that do not harm the patient. Additionally, cost needs to be evaluated due to the principle of beneficence and the principle of justice. The physician ought to provide the least costly treatment first in order for more patients to have access to treatment. Moreover, by examining cost, the physician is taking into account the other financial responsibilities that the patient may have to themselves or to their families. Another reason this framework examines cost because high cost is also one of the signals for scrutiny that Largent (2009) provides for off-label use.

Phantom Limb Pain Treatments

Below, I fill in the charts provided in accordance with the types of treatments that are available for phantom limb pain. Even though clarifications for the rankings will be provided, chapter two should be referred to for more in-depth descriptions and studies of the treatments. It should also be noted that while not all categories are filled in, it is important for them to be present in case a new treatment becomes available.

Evidence Labels.

Table 3

Phantom Limb Treatments Placed in Evidentiary Categories

Evidentiary Categories	Treatments
Supported	None
Suppositional	Mirror Therapy Opioids NMDA Receptor Antagonists NSAIDs Acetaminophen TENS Unit Spinal Cord Stimulation Bupivacaine
Investigational	Anticonvulsants Antidepressants Acupuncture Botulinum toxin type A Lidocaine Spinal Cord Stimulation Stump Revision Deep Brain Stimulation

At the current time, no treatment exists for phantom limb pain that falls under the supported category. This is because, currently, all of the research done on the treatment of phantom limb pain includes small numbers of participants, case studies, and conflicting evidence (Alviar et al., 2016; Ehde et al., 2000; Pérez-Cruzado et al., 2017). For this reason, no treatments have a moderate to a high degree of certainty of net benefit.

In terms of the investigational category, anticonvulsants, antidepressants, acupuncture, botulinum toxin type A, and lidocaine have all been placed category due to their conflicting research and limited support for pain relief (Alviar et al., 2016; Bone et al., 2002; Trevelyan et al., 2016; H. Wu et al., 2012). Additionally, drugs such as anticonvulsants and antidepressants fall under the novel off-label use category because their approved labeling is not involved in pain management (Bone et al., 2002; Hall, Carroll, & McQuay, 2008).

Looking further into the investigational category, stump revision, spinal cord stimulation, and deep brain stimulation have been placed here due to their high potential for harm and low potential for net benefit. Additionally, all three of these treatments are surgical, and thus are high in cost (Bell, Mathieu, & Racine, 2009). Due to this high cost, they fall under the signal for scrutiny of drugs (or treatments). Additionally, surgical treatments have known adverse side effects. Stump revision surgery is successful in relieving stump pain by removing neuromas and other causes of the pain but sees very little success in the relief of phantom limb pain (Tintle et al., 2012). As with any surgery, there can be adverse side effects in the way of various complications including infection, blood clots, reaction to anesthesia, and many others (Tintle et al., 2012). Spinal cord and deep brain stimulation have a large degree of potential harm for these same reasons with the additional confound that they involve implantation of an electrode in the brain or spinal cord (Abreu et al., 2017; Maslen et al., 2018; Viswanathan et al., 2010). Each of these is not well researched in terms of phantom limb pain but has been successful in the relief of other types of chronic pain (Farrell et al., 2018; Smits et al., 2013). For these reasons, I argue that these treatments should be reserved for prescription after the suppositional categories have failed to treat the patient's symptoms and these treatments should be performed in a research setting only.

Suppositional Expanded.

Table 4

Suppositional Treatments for Phantom Limb Pain in Order of Use

Order of Use	Treatments
1st	Mirror Therapy TENS unit
2nd	NMDA Receptor Antagonists NSAIDs Acetaminophen
3rd	None
4th	Bupivacaine Opioids

The treatments that I have placed in this category span a wide range of options from medication to injections or physical therapy. In general, these are the most commonly used treatments for phantom limb pain, and for these reasons they have the most research available. However, most of the indicators are not from randomized or double-blind trials, but rather patient surveys (Baron, Wasner, & Lindner, 1998; L. Nikolajsen & Jensen, 2001).

Starting from the bottom and looking at the fourth line of use, both an injection and opioids are fairly expensive, especially if the patient does not have insurance (Zezza

& Bachhuber, 2018). Bupivacaine requires a professional for the injection, and opioids require a lifetime prescription. Additionally, these medications have a relatively high potential for harm as compared to others in the suppositional category. For example, bupivacaine can cause permanent numbing if injected wrong (Nikolajsen, Ilkjaer, Christensen, Krøner, & Jensen, 1997). For opioids, they have numerous adverse side effects including addiction, dizziness, nausea, etc. (Wilder et al., 2016).

Currently, there are no treatments in the third line of prescription which are high risk and low cost. Moving up to the second line of use, many of the common prescriptions for phantom limb pain can be found including NSAIDs and acetaminophen (Stockburger et al., 2016). Low-cost versions of these drugs can be found over the counter placing them into this category. In terms of risk, both drugs have potential harms such as liver failure, gastrointestinal and cardiovascular problems (Hanley et al., 2006; Salvo et al., 2011).

The two treatments that fall into the low risk and low-cost category are transcutaneous electrical nerve (TENS) units and mirror therapy. These two treatments have some research demonstrating their ability to decrease phantom limb pain (Tilak et al., 2016). Additionally, after being taught how to perform mirror therapy or how to use a TENS unit by a physical therapist, the individual can perform the therapy whenever they want with little cost to them (Mulvey et al., 2010; Pérez-Cruzado et al., 2017). One differentiating factor between the two treatments is that TENS unit alleviates the pain for only a short duration (hours), while mirror therapy has some potential for its effect to last longer (days; Casale et al., 2009; Köke et al., 2004)

What This Means for the Prescription of Treatment

In the midst of not understanding the mechanisms behind phantom limb pain, medications have found themselves at the forefront of pain treatment (Stockburger et al., 2016). As we return to biomedical ethics principles, increased prescription of in pain medication (often in increasing dosage) in those with phantom limb pain prior to trying less risky alternatives goes against the principle of nonmaleficence. In these cases, the health care provider is potentially doing the patient more harm than good when there are other options available.

The previous chapter went into great depth on the treatment of phantom limb pain with mirror therapy. It can be seen from the framework provided why this is so. For one, mirror therapy is relatively inexpensive. While mirror therapy must be done with a physical therapist for a few sessions, after learning how, a patient can perform the technique by themselves. If effective, this decreases the cost of the treatment compared to other traditionally prescribed options such as opioids. As such, mirror therapy follows the principle of beneficence in treatment. If the treatment is successful, they can return to their daily activities with very little monetary cost to them and avoid the risky side effects of opioids such as addiction, nausea, etc. Furthermore, this increases the number of individuals who have access to the treatment, and for this reason, follows the principle of justice.

Looking further into the principle of justice, these individuals are often from a vulnerable population. As discussed earlier, mental illness is frequently comorbid with chronic pain (Benjamin et al., 1988). Furthermore, those with phantom limb pain are even more vulnerable due to the fact that their pain can be associated with a traumatic event (Cavanagh et al., 2006; Desmond & MacLachlan, 2006). Prescription of opioids could make their condition worse if they are suffering from post-traumatic stress disorder or depression (K. Z. Smith, Smith, Cercone, McKee, & Homish, 2016). Because of this, treatments with less risk associated with them should be considered first when looking at the phantom limb population.

While I have argued for low-risk and low-cost treatment options to be presented and discussed with the patient first, just like in Largent's (2009) framework, I maintain that the choice should be up to the patient. The framework that is provided is one that clinicians can turn to when prescribing treatment for phantom limb pain. I maintain that the treatments should be presented in the order described by the framework, but the framework should not be the only viewpoint that the clinician should examine. In other words, the clinician should consider the patient's opinions when making treatment decisions. This is based on the principle of respect for autonomy. As described earlier, the patient understands their pain and their own risk aversion better than anyone else (McCaffery & Beebe, 1989).

Phantom limb pain, and is treatments are not well understood, and the patient should understand this concept. Because all of the treatments available for phantom limb pain currently fall in the suppositional category, a clinician should have a conversation with the patient that discloses all the risks and benefits of the treatment being provided. The patient should work with the physician to recognize the harm-benefit ratio for any treatment. This ratio, which falls under the principle of nonmaleficence, may be weighed differently in the patient's eyes. If the patient decides they want to take a more drastic approach, due to the intensity of their pain or some other reason, similar discussions should take place as they move down the lines of treatment. In order to ensure the patient receives this type of treatment plan, a further recommendation of a team-based approach to treatment needs to be discussed.

Practical Recommendation

To ensure that patients receive information about multiple treatments and understand the harm-benefit ratio of each, more voices should be brought into the treatment of phantom limb pain. While cancer pain and phantom limb pain are two very different types of pain, as discussed earlier, they are both subjective experiences which are similar in the fact that they are both complex in their mechanisms and treatment (L. Nikolajsen & Jensen, 2001; Robb et al., 2010). For this reason, this section will use one of the guidelines put forth by cancer pain treatment that could aid in the treatment of phantom limb pain.

Team-Based Approach

One guideline set forth for cancer-related pain, but seems to be lost in the treatment of phantom limb pain, is "a collaborative, interdisciplinary approach to the care of patients" (Jacox et al., 1994, p. 651). With this collaborative approach, an individualized treatment plan for the patient can be created. The patient can be actively engaged in their treatment plan because they are thought of as a member of the team. For the purposes of this discussion, it can be assumed that most individuals with phantom limb pain meet the criteria discussed above for informed consent. This is due to the fact that most of these patients' comorbidities with amputations are of a physical nature (Foote et al., 2015; Wukich & Pearson, 2013). For this reason, this approach to treatment increases the autonomy a patient has throughout their treatment. A patient receiving treatment for cancer pain has not only an oncologist on their team, but a pharmacologist, physical/occupational therapist, and psychiatrist/psychologist. Similar to this cancer guideline, this approach is currently being expanded to the treatment of other chronic pain disorders (Gatchel, McGeary, McGeary, & Lippe, 2014). In the treatment of phantom limb pain, I believe that there are two key voices that are not present: a psychologist and a physical therapist. These two core positions can increase the principle of beneficence in these patient's care. Both positions serve as key advocates for patient safety and wellbeing.

Psychologist/Psychiatrist

I recommend a psychologist/psychiatrist joining the team due to the likelihood of patients developing a mental illness while experiencing phantom limb pain (Ahmed et al., 2017). In the interdisciplinary team, a psychologist's role is to "provide a full psychosocial evaluation" and "Assess [the] patient's psychological strengths and weaknesses" (Gatchel et al., 2014, p. 124). In doing so, the psychologist is examining the mental health of the individual and helping them through any mental illnesses they may have. In regards to patients with phantom limb pain, there is an increased prevalence of depression that should be addressed by a psychiatrist (Ahmed et al., 2017). Specifically, body image and decreased self-esteem in these patients could play a role in this depression for individuals (Atay, Turgay, & Atay, 2014). While this particular article by Atay, Turgay, and Atay (2014) finds the relationship between decreased self-esteem and depression with individuals using a prosthesis, it can be assumed that there is a similarity without prosthesis use. Because pain interpretation is, in part, emotionally based, and due to the high comorbidity of depression, phantom limb pain patients should have a psychologist/psychiatrist on their team as well.

Physical Therapist

I recommend a physical therapist to join the team in the treatment of phantom limb pain. While physical therapists are commonly utilized in the treatment of amputees during prosthesis training, they should further provide a role in pain management (Cole, 2003). It should be noted that phantom limb pain is not the only pain experienced by patients after an amputation. They can also experience stump pain, which is coming from amputation (T. S. Jensen et al., 1983). A physical therapist can encourage the treatment of these pains through noninvasive techniques. Some techniques that could be suggested include a transcutaneous electrical nerve stimulation (TENS) unit or mirror therapy (Tilak et al., 2016). These treatments provide an alternative for any patient, but particularly those who do not want to become dependent on medications or endure drastic measures for the alleviation of their pain.

Summary

In implementing a team-based approach to treatment, the respect for autonomy for the patient in their treatment will be increased. The voices of a psychologist/psychiatrist and a physical therapist will provide better treatment for phantom limb pain. These voices will aid in providing different explanations for the reasons behind the pain, as well as treatment options beyond the medications commonly provided. As such, the patient will have a more positive and ethically informed treatment experience.

Conclusion

This chapter began with introducing common morality principlism, which served as an introduction to bioethical theory. The chapter then introduced the problem with pain treatment in general but narrowed down on the specifics of phantom limb pain treatment. In order to examine the treatments that exist, and the treatments that may come forth, a framework based on the framework presented in "Going off-label without venturing off-course: evidence and ethical off-label prescribing" by Largent (2009) was presented. This, in conjunction with common morality principlism, allowed the ethical evaluation of the treatments available for phantom limb pain. While this is just one way to examine phantom limb pain, it provides a framework to help guide clinicians through the treatments of phantom limb pain. This framework argues that the first treatment that should be presented to a patient is that of mirror therapy, with other noninvasive treatments and medications to be presented subsequently. With this being said, the framework is just a tool, and the choice should be ultimately up to the patient. This evaluation of treatment further highlighted the need for an interdisciplinary team, including a psychologist/psychiatrist and physical therapist in order to effectively treat this complex disorder.

CONCLUSION AND REFLECTIONS

As we look forward from this exploration of phantom limb pain and its treatment, I would like to make some concluding remarks. First, I would like to explore what I see as a potential cause of phantom limb pain and how this could be examined in a research setting. Secondly, I would like to broaden what the treatment of phantom limb pain means for the investigation and treatment of other disorders. In particular, I would like to explore how this thesis has changed the way I think of treatment as I soon approach the next portion of my education, pursuing my degree as a Doctor of Physical Therapy.

The Visual Side of Phantom Limb Pain

In his book *Phantoms In The Brain*, Ramachandran (1996) discusses the impact of visual feedback on phantom limb pain. Ramachandran explains that the brain is sending out signals for the amputated limb to move, but the brain does not receive any sensory or visual feedback that the arm is actually moving. After this repeated signaling the brain comes to a state of "learned paralysis" as the inability to move is "stamped onto the brain's circuitry" (Ramachandran & Blakeslee, 1998, p. 46). In other words, the brain creates a memory that this limb is immobile. Ramachandran then proposes mirror therapy as a way to "trick [the] eyes into actually seeing a phantom," (Ramachandran & Blakeslee, 1998, p. 46). While Ramachandran mostly abandons the talk of the impact of the visual system and returns to the theory of remapping and maladaptive plasticity, I believe he may be missing a key component to phantom limb pain.

While the theories present for phantom limb pain presented in Chapter 2 are backed by support, none of them tell the whole story. Furthermore, they do not fully explain why mirror therapy serves as an effective treatment (Young Kim & Young Kim, 2012). In examining the relief that mirror therapy provides, it does induce changes in the somatosensory cortex after four weeks of treatment (Foell et al., 2014). As such, when mirror therapy is applied there is a reduction between the asymmetry of the two hemispheres. This change supports the theory of central nervous system maladaptive plasticity because these changes correlate with phantom limb pain reduction. It does not, however, explain the instantaneous relief that some patients receive from mirror therapy after one session. Ramachandran describes that the "digging sensation" in one individual was eliminated during his first time using the mirror (Ramachandran & Blakeslee, 1998, p. 53). Additionally, this same relief in phantom limb pain is seen after five sessions or one week of treatment (Chan et al., 2007; Finn et al., 2017). For this reason, the visual system's impact and the conflicting signals the brain is receiving while experiencing phantom limb should be expanded upon.

One such example can be found in the theories behind motion sickness. One proposed explanation for motion sickness is called sensory conflict theory. This theory proposes that a mismatch is occurring between the visual and vestibular sensations in regards to the experience of motion (Kohl, 1983). For example, when an individual is reading a book in a car. Their eyes are not sensing movement, but their vestibular system is sensing the forward movement of the car. Further investigations of motion sickness have supported the role of both systems in the disorder (Ishak, Bubka, & Bonato, 2018;

Warwick-Evans, Symons, Fitch, & Burrows, 1998). Due to this mismatch, the individual experiences nausea, lethargy, and other symptoms of motion sickness.

I propose a theory that phantom limb pain may have a similar sensory conflict with slightly different systems. While the conflict is still due to a visual system mismatch, the mismatch occurs with somatosensory information. The brain does not "see" an arm, like Ramachandran discusses, but is still receiving somatosensory input. This somatosensory input could be in the form maladaptive plasticity in the central nervous system or input from severed peripheral nervous system fibers. One way to investigate this hypothesis would be to explore whether there is a reduced frequency, or decreased intensity, of phantom limb pain in patients that are blind. While this may seem like a small portion of individuals, blindness and amputations are both complications of diabetes and perhaps likely of various forms of war trauma such as with IED explosions. This component of phantom limb pain does not discount the other theories developed; instead, it adds to the discussion of other confounding factors that could influence pain. While developing an experiment is outside the scope of this thesis, these factors warrant further research.

Expanding Outward

As I hope this thesis has demonstrated, phantom limb pain is a difficult disorder to understand and treat. This difficulty is not just felt by those attempting to research and treat the disorder, but by those who experience it. These individuals are who this thesis intends to benefit. At this time, I would like to demonstrate the difficulty that phantom limb pain brings to individuals through some quotations.

In an article by Nortvedt and Engelsrud (2014), the authors record the words and capture pain felt by individuals who have lost a limb. One man who lost his arm to a motorcycle accident describes his excruciating phantom limb pain as such:

> It’s as if the skin of my arm has been ripped off; salt is being poured on it and then it’s thrust into fire. I also sometimes feel as if the fingers on my amputated hand are moving uncontrollably, which is both extremely painful and embarrassing (Nortvedt & Engelsrud, 2014, p. 602).

It is hard for any of us to imagine dealing with that kind of pain on a day-to-day basis. While this is just one description, it provides an example of the intensity of pain that these individuals feel while experiencing phantom limb pain. A type of pain that no scale nor physician could begin to understand.

In the same article, a man addresses his depression that results from phantom limb pain:

> It’s constant as if I have a big, strange object growing out on my head that I can’t get rid of. It’s always there and it drives me crazy. It does something terrible to me. I can’t concentrate on anything but the pain. If I read a book I can’t concentrate on the text and I don’t remember what I’ve read. I can’t go on living like this (Nortvedt & Engelsrud, 2014, p. 604).

This quote is striking in that it really puts into context how the pain can affect these individuals' lives. An everyday activity, such as reading, can be impaired by phantom limb pain. This debilitation, among other factors, leads to depression in these individuals (Ephraim, Wegener, MacKenzie, Dillingham, & Pezzin, 2005). This is why examining the pain, and looking for the best way to treat it, is so important for these individuals.

Moreover, the ideas presented in these quotations expand further than just phantom limb pain, but to others who experience other debilitating chronic pain disorders. Fibromyalgia, complex regional pain syndrome, migraines, dystonia, and restless leg syndrome are just a sampling of disorders, similar to phantom limb pain, where the cause is unknown and the treatment is complex and riddled with an array of pain killers (Buse et al., 2012; Garcia-Borreguero, Cano-Pumarega, & Marulanda, 2018; Mackey & Feinberg, 2007; Painter & Crofford, 2013; Srinivasan, Lim, & Thirugnanam, 2007). Similar to phantom limb pain, the chronic pain in these disorders can become debilitating to the individual's life.

Because of this, I hope that this thesis brought forth the idea that more research should be done into both the mechanisms and treatments of phantom limb pain and related disorders. While it is important to look at and examine further treatments of these disorders, I believe that more focus needs to be put on the mechanisms of phantom limb pain and related disorders. In doing so, the similarities and differences between chronic pain disorders can be discovered. From there, more individualized treatment plans for these disorders can be formalized. Because, as seen with the case of phantom limb pain, treatments such as opioids and NSAIDs that work well in relieving many types of pain, do not work well when it comes to this disorder.

I also hope that my thesis brings forth a framework for treatment that can be utilized by clinicians when treating phantom limb pain, and other disorders where there is limited research on the mechanisms and treatment of the disorder. This thesis began as an exploration of the interaction between phantom limb pain and mirror therapy and ended with me discovering that I believe it truly should be the first place that treatment should start. Through this thesis, I found that physicians often prescribe medications with multiple side effects as a way to help alleviate the pain, even though there is little research to support them. This is true despite the fact that minimally invasive, low-cost treatments, like mirror therapy, are available that have similar degrees of support as the medications.

This thesis has illuminated for me the complexities that arise when examining how to treat a patient. While I understand it has only scratched the surface of these difficulties, it has shown me how to begin to weigh the pros and cons of various treatments when limited information is available. As a future physical therapist, I hope to become an advocate for patients with disorders, such as phantom limb pain, that are not well understood. As such, I hope to endorse and advance the noninvasive treatment options that my future occupation has to offer.

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