MDH Minnesota Department *of* Health
OFFICE OF MEDICAL CANNABIS

Phantom Limb Pain

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Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicatrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Phantom limb pain (PLP) is pain that is experienced in a missing or amputated limb. Essentially, patients who experience PLP experience pain in a region of the body that no longer exists (due to amputation) or never existed (for example, in cases of congenital limb deficiency). This is not to be confused with residual limb pain (a.k.a. stump pain), which is pain that is experienced in the remaining part of the limb (Merskey & Bogduk 1994). Currently, there are no medical tests specifically used to diagnose PLP (Mayo Clinic). Instead, physicians can identify this condition based on the patient's medical history and circumstances leading up to the

phantom pain sensations in the affected body region(s). PLP has been described in many different body parts, including upper and lower limbs, breasts, eyes, and genitals (Sherman et al. 1984, Hansen et al. 2011, Rasmussen et al. 2011, Wade & Finger 2010). The suffering and trouble caused by PLP has been described as "moderate" to "very much" in 65% of patients (Kooijman et al. 2000), with just under 70% rating typical PLP at moderate to severe levels (between 4-10 on a 0-10 numerical rating scale; Sherman et al. 1984). Descriptions of PLP vary including stabbing, electric shock-like, pins and needles, tingling, squeezing/crushing (Sherman et al. 1984; Wartan et al.1997).

Prevalence

Not all patients with an amputation or missing limb will experience PLP. Estimates on the prevalence of PLP have ranged from roughly 50-80% of amputees (Sherman et al. 1984, Kooijman et al. 2000, Wartan et al. 1997, Houghton et al 1994), with significantly lower numbers (~4%) being reported for patients with congenital limb deficiency (Wilkins et al. 1998). Moreover, because the number of individuals undergoing limb amputation is expected to grow over time in the US (Ziegler-Graham et al. 2008), the sheer number of patients experiencing PLP will undoubtedly grow in parallel. According to 2005 national estimates, there were 1.6 million people with limb loss, and those numbers are expected to at least double by 2050 (Ziegler-Graham et al. 2008).

Current Therapies

Both pharmacologic and non-pharmacologic treatments are currently used for managing PLP. Overall evidence for pharmacologic interventions is mixed on efficacy, while mind-body therapies – while promising – would benefit from greater study and follow-up of patients over time. This section will cover the more common therapies found in these domains.

Pharmacologic treatments

Available pharmacotherapies for PLP patients widely vary because there is no one mechanism that is consistently thought to be solely responsible for generating PLP. Therefore, drug targets are derived based on the current understanding of what particular mechanisms may be involved in generating PLP. Currently, a few different peripheral and central mechanisms are proposed to underlie PLP, which includes changes induced by neuromas that develop post-amputation, changes in the spinal cord at the dorsal horn, as well as cortical reorganization in somatosensory cortex (Flor et al. 2006; McCormick et al. 2014; Subedi & Grossberg 2011). Drugs acting on peripheral mechanisms typically inhibit nerve impulses, which includes bupivacaine and ropivacaine. However, there is mixed evidence for their efficacy in treating PLP (McCormick et al. 2014). Amitriptyline, a tricyclic antidepressant which is thought to have peripheral analgesic effects, has also been used with moderate to no effect on PLP (Alviar et al. 2011; McCormick et al. 2014). Opioids are also sometimes used, which has been moderately to highly successful in reducing PLP short-term (Alviar et al. 2011). There has also been some research to prevent the development of PLP with an epidural administration of an opioid and nerve blocks just before amputation (preemptive analgesia). This, however, has

also shown mixed efficacy across studies (McCormick et al. 2014). Botulinum toxin Type A injections at the site of the residual limb have also been explored, but the evidence for relieving PLP has been weak or restricted to small sample sizes (Wu et al. 2012; Jin et al. 2009).

Central mechanisms responsible for PLP point to neuroplastic changes at the dorsal horn and somatosensory cortex. For example, the dorsal horn shows evidence of sensitization after amputation as well as spinal reorganization of afferent signals in this region (Flor et al. 2006). Reorganization at the somatosensory cortex may also contribute to PLP. After amputation, the somatosensory region responsible for representing the amputated limb no longer serves a functional purpose; therefore, adjacent somatosensory regions "invade" leading to abnormal circuitry that may lead to the development of PLP. Treatments targeting central mechanisms are typically antiepileptic drugs (AEDs) to counteract hyperexcitability in the central nervous system. Evidence for the efficacy of AEDs (particularly gabapentin and topiramate) – while promising – is mixed (Alviar et al 2011; McCormick et al. 2014).

Non-pharmacologic treatments

There is some literature to suggest that mind-body therapies may provide some benefit to treating PLP. Mind-body therapies take advantage of the connection between the mind and body by trying to alter physical functioning and experience (i.e., pain) through mind and behavior. While literature is sparse in the use of mind-body therapies for specifically treating PLP (Moura et al. 2012), the ones most commonly found were mirror visual feedback therapy, guided imagery, hypnosis, and biofeedback techniques.

Mirror visual feedback therapy has been most well-studied out of all mind-body therapies to specifically treat PLP. Traditionally, this therapy involves a patient placing their non-amputated limb into a box containing mirrors which then gives the perception that the amputated limb has been restored (Ramachandran & Altschuler 2009). However, there are also studies that have effectively used virtual feedback to give the perception of limb restoration and functionality (Mercier & Sirigu 2009). While visual feedback therapy has been found to alleviate PLP to some degree, evidence from randomized trials is relatively sparse (Chan et al. 2007) with most evidence coming from case series/reports or non-randomized trials (Moura et al. 2012).

Guided imagery techniques have also been used for treating PLP, which requires patients to immerse themselves into their senses through mental imagery and imagination. In the case of PLP, this often means using mental imagery on the phantom limb to imagine sensations or movement to alleviate pain. Evidence for the efficacy of this technique, while showing some promise, is sparse (Moura et al. 2012).

There are a few studies using hypnosis for treating PLP with some efficacy, but again, studies are also sparse for this technique and could benefit from more rigorous study (Moura et al. 2012). Lastly, biofeedback therapy (involves using biofeedback instruments to bring to

awareness autonomic nervous system dysregulation) has some data on reducing PLP (Moura et al. 2012). However, very few studies of this type exist and are underpowered.

Pre-Clinical Research

No preclinical evidence was found regarding the use of cannabis to specifically treat PLP. While preclinical studies investigating the effects of cannabis and cannabinoids on pain is found in the literature, these studies group PLP under neuropathic pain which makes any interpretation of treatment efficacy nearly impossible without concerted efforts to stratify results by this patient group.

Clinical Trials

As of mid-August 2016, only one clinical trial has been identified that examines the efficacy of cannabinoids on specifically treating PLP. However, this study – while listed as completed on the website – has not been updated on ClinicalTrials.gov to include study results, nor have any publications been found relating to this study. This particular study was a randomized, double-blind clinical trial investigating the effects of nabilone (Cesemet; synthetic analogue of THC) on the management of pain and quality of life in phantom limb patients. Study participants were assigned nabilone or placebo (parallel assignment) with primary and secondary measures collected at baseline, 2, 4, and 6 weeks of treatment. The primary outcome measure was scores on the visual analogue scale for pain. Secondary outcome measures were scores on 1) Depression Anxiety and Stress Scale, 2) Groningen Sleep Quality Scale, 3) SF-36, 4) frequency of phantom limb pain, and 4) daily prosthetic wearing time. Study details can be found at Nabilone for the Treatment of Phantom Limb Pain https://clinicaltrials.gov/show/NCT00699634

Observational Studies

No observational studies have been identified that specifically address pain management in PLP patients with cannabis. While there are several studies investigating the effects of cannabis and cannabinoids on neuropathic pain patients, many of these studies do not stratify their results by neuropathic pain type/cause (i.e.., PLP). Therefore, there is a gap in knowledge within this particular patient group.

There is one survey study by Dunn and Davis (1974) that did measure the effects of cannabis on PLP in spinal cord injured males. Of the nine (out of 10) patients experiencing phantom pain, four (44%) experienced a decrease in PLP, while one patient (11%) showed an increase in PLP. Another two patients (22%) showed no effect of cannabis on PLP, while another two (22%) indicated that cannabis helped distract from PLP while not reducing actual PLP. However, it should be noted that this was an informal survey conducted on a small sample within one hospital in the US. Details on survey methodology were also omitted in this publication. Lastly, because the patient sample all had spinal cord injuries, results are even further restricted to apply to an even smaller subset of PLP patients (PLP patients with spinal cord injuries).

National Medical Organization Recommendations

No guidance documents or recommendations from national medical organizations for the therapeutic use of cannabis or cannabinoids in the management of PLP were found.

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