The Effect of Pregabalin in Patients with Phantom Limb Pain: A Randomized Controlled Trial

Brandon Beattie
beattie228@gmail.com

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THE EFFECT OF PREGABALIN IN PATIENTS WITH PHANTOM LIMB PAIN:
A RANDOMIZED CONTROLLED TRIAL

A Thesis Presented to
The Faculty of the School of Medicine
Yale University

In Candidacy for the degree of
Master of Medical Science

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Brandon Beattie, PA-SII
Class of 2015
Yale Physician Associate Program

Huned S. Patwa, MD
Associate Professor
Department of Neurology
Yale School of Medicine
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ABSTRACT

Phantom Limb Pain is perceived pain in a region of the body that has been removed through amputation. It is a devastating syndrome affecting up to 80% of all post-amputation patients, however, no reliable treatment option currently exists. Pregabalin is proven to be effective in the treatment of similar symptoms of a diabetic neuropathic origin. We propose a double-blinded, randomized controlled trial to evaluate the effect of pregabalin in patients who experience Phantom Limb Pain. We expect the pregabalin treatment to produce a statistically significant change in mean pain from baseline as well as an improvement in quality of life factors in individuals suffering from Phantom Limb Pain. If proven effective, pregabalin will provide a crucial treatment option for patients who experience Phantom Limb Pain.
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Chapter One: Introduction

1.1 Background

The term Phantom Limb Pain (PLP) is defined as pain perceived in a region of the body that is no longer present due to amputation.\textsuperscript{1} It is a devastating syndrome marked by persistent pain within an amputated limb affecting 80\% of all post-amputation patients regardless of whether the amputation has occurred in an upper or lower limb.\textsuperscript{1-5} Symptoms generally include: burning, throbbing, aching, cramping or stabbing pain with sharp and stabbing pain noted as the most common forms of presentation.\textsuperscript{1-3,6} PLP can be debilitating for the patients experiencing this unique type of pain due to immense suffering and significant decrease in quality of life.\textsuperscript{7}

PLP was first described in the 16\textsuperscript{th} century by the French military surgeon Ambrose Pare with the actual term Phantom Limb Pain coined in the 19\textsuperscript{th} century by Silas Weir Mitchell, a famous Civil War surgeon.\textsuperscript{2,5,8} Once thought to be psychiatric in origin, the accumulation of recent research findings has shown the cause of PLP to be related to peripheral and central neural mechanisms, while psychological factors seem to influence the overall course and severity of the pain.\textsuperscript{2,5} As is the case with most neuropathic pain syndromes, diagnosis relies almost entirely on the history and physical examination.\textsuperscript{9}

A recent study estimated there were roughly 1.6 million people with limb loss in the United States in 2005; this number is expected to increase to 3.6 million people by the year 2050.\textsuperscript{2} Furthermore, the number of traumatic amputations as a result of military conflict in Iraq and Afghanistan has contributed significantly to the increasing rise of amputees within the veteran population.\textsuperscript{2} Since the start of the conflicts in Iraq and
Afghanistan, over 900 amputees have been treated at Walter Reed Army Medical Center in Washington, D.C. While PLP has increased due to amputations related to military conflict, PLP is not limited to just these cases. Diabetic patients who experience PLP after a surgical amputation appear to have a similar incidence, prevalence, and level of pain as compared to those individuals who have undergone a traumatic amputation. The most commonly reported reasons for limb loss include vascular problems, trauma, cancer and congenital limb defects.

The complex etiology of PLP and overwhelming nature of the symptoms can make the management of PLP patients very frustrating for clinicians. A variety of treatments have been proposed, however, evidence-based guidelines for treatment are lacking, due in large part to the absence of properly controlled clinical trials. Treatment modalities currently utilized by clinicians include pharmacologic and non-pharmacologic approaches, though often with poor results. Pharmacotherapy modalities include opioids, tricyclic antidepressants such as Amitriptyline and N-methyl-D-aspartate (NMDA) receptor antagonists such as Memantine as well as nonsteroidal anti-inflammatory drugs (NSAIDs). A cross sectional study found acetaminophen and NSAIDs to be the most common medications used in the treatment of PLP however trial results have been poor, especially in individuals who describe their pain to be moderate to severe. Non-pharmacologic modalities include noninvasive therapy such as mirror therapy and biofeedback, as well as invasive surgical procedures which include stump revision and rhizotomies. Controlled studies investigating treatments for PLP are generally lacking, but a limited number of clinical trials have shown a maximum benefit of about 30% from these treatment modalities, a proportion which does not exceed the
placebo effect.\textsuperscript{5,6,11} A summary of currently proposed treatments for PLP is found in Table 2.1.

Nociceptive pain usually responds well to traditional analgesics while neuropathic pain is much less responsive to most medications, making the treatment of PLP much more difficult to manage.\textsuperscript{6} Specific mechanism-based treatments are still evolving as most treatments for PLP are based on neuropathic pain trials.\textsuperscript{2} Previous studies researching the use of anticonvulsants, such as pregabalin and gabapentin, have been shown to be effective in the treatment of similar painful neuropathic syndromes such as painful diabetic peripheral neuropathy and post-herpetic neuralgia. No studies have been performed to date, however, investigating the effect of these medications in the treatment of painful symptoms related to PLP.\textsuperscript{12-14}

1.2 Statement of the Problem

No reliable treatment option currently exists for the treatment of symptoms related to PLP.\textsuperscript{9} Current treatment options are left to clinician discretion and no standardized guidelines exist. This is likely due to the lack of evidence-based medicine with these treatment options having little to no effect on painful symptoms or overall quality of life.\textsuperscript{6} Previous studies have exhaustively researched the use of anticonvulsants, such as pregabalin and gabapentin, for the treatment of painful neuropathic syndromes like diabetic peripheral neuropathy and post-herpetic neuralgia and these medications appear promising for the treatment of PLP.\textsuperscript{12-14}

When taking into account that 80\% of all individuals with an amputation will experience PLP at some point in their lives, it is clear to see the tremendous impact this
syndrome has on an increasingly larger percentage of the general population.\textsuperscript{1,2,5} The literature contains a few scattered case reports, case series and letters to the editors with extremely underpowered studies attempting to investigate treatment modalities for PLP yet few high-quality randomized controlled trials exist to-date.\textsuperscript{8} PLP remains a somewhat poorly understood and difficult to treat medical condition with a wide variety of different treatment regimens employed but mechanism-based treatment guidelines have yet to evolve.\textsuperscript{2} Given the incredibly high prevalence, age of onset and decreased quality of life due to limited effective treatment options for PLP, further studies are clearly needed.

1.3 Goals and Objectives

This study aims to investigate the effects of pregabalin on symptoms related to PLP in amputee patients. The primary outcome of the study will be the mean decrease in pain from baseline after 15 weeks of pregabalin intervention versus placebo. The primary outcome will be measured via the Numeric Rating Scale (NRS) Tool for Self-Reporting of Pain where 0 is no pain and 10 is the worst possible pain. Secondary outcomes of the study will be the mean increase in quality of life measurements from baseline after 15 weeks of pregabalin intervention versus placebo. The secondary outcomes, which will include physical functioning, social functioning, role limitations attributable to physical problems and general mental health, will be measured via the SF-36 (Short Form) Health Survey. If proven effective, pregabalin could provide a crucial treatment option for amputee patients who experience symptoms related to Phantom Limb Pain.
1.4 Hypothesis

Primary Hypothesis

Among patients experiencing symptoms related to PLP, a mean decrease in pain from baseline to 15 weeks will be noted in participants who receive pregabalin treatment as compared to a placebo control group. Pain symptoms will be assessed at baseline as well as weekly for 15 weeks via an Interactive Voice-Response (IVR) System using the NRS Tool For Self-Reporting of Pain and a daily pain diary. Medication compliance will be monitored using Radiofrequency Identification (RDIF) technology.

Secondary Hypothesis

Among patients experiencing symptoms related to PLP, there will be a mean increase from baseline in quality of life measures to include:

a) Physical functioning, assessed by the SF-36 Health Survey, as compared to the placebo control group after 15 weeks of intervention.

b) Social functioning, assessed by the SF-36 Health Survey, as compared to the placebo control group after 15 weeks of intervention.

c) Role limitations attributable to physical problems, assessed by the SF-36 Health Survey, as compared to the placebo control group after 15 weeks of intervention.

d) General mental health, assessed by the SF-36 Health Survey, as compared to the placebo control group after 15 weeks of intervention.
1.5 Definitions

- **IVR (Interactive Voice-Response) System**: Automated voice response system where study participants record daily pain scale and sleep diary results as well as report the total number of medication doses taken throughout the day.\(^{15}\)

- **NRS (Numeric Rating Scale) Tool For Self-Reporting of Pain**: One of the most common measures of pain intensity used by clinicians and researchers alike.\(^{16}\)

- **RFID (Radiofrequency Identification) Technology**: Novel compliance monitoring system that embeds RFID tags into prescription blister packaging to allow for direct electronic monitoring of the date and time a patient or research participant opens a medication package.\(^{17}\)

- **SF-36 (Short Form Health Survey)**: Quality of life instrument for measuring health perception in a general population.\(^{18}\)
References


Chapter Two: Literature Review

2.1 Introduction

An extensive review of the medical literature was performed using Ovid MEDLINE and PubMed to review high quality peer-reviewed articles from 1946 through June 2015. Search results were limited to reviews and randomized controlled trials and then further narrowed down to include only articles written in English. Furthermore, articles were only included in the final literature review if they were peer-reviewed articles involving the use of adult human subjects. A final search of the literature was completed on June 22, 2015.

Keywords used to complete the literature review included *Phantom Limb Pain*, *pregabalin* or *Lyrica*, *acetaminophen*, *Diabetic Neuropathies*, *pain measurement* and *pain instrument*. The aforementioned keywords were then combined in a number of ways using the search features found in PubMed. While a majority of the articles were from United States publications, a very small number of international articles were included in the literature review. Initially, articles were examined based on the title and abstract to ascertain their relevancy to the proposed study. Once articles were screened using these parameters, full text versions of the articles were obtained and thoroughly examined for relevancy and applicability.
2.2 Review of the Relevant Literature

*Phantom Limb Pain*

High quality randomized controlled trials investigating the treatment of PLP are severely lacking in the literature.¹ In 2002, Bone et al. attempted to examine the effectiveness of gabapentin in the treatment of PLP in a placebo-controlled cross-over trial with a one-week wash-out period. Randomization was achieved via computer-generated randomization. Participants consisted of patients with PLP for greater than 6 months with an average pain intensity greater than 40/100 on the VAS (Visual Analog Scale). A total of 19 subjects (15 males versus 4 females) participated with a mean age of 56.25 years and a baseline mean pain intensity of 6.1/10. Interventions included gabapentin titrated in increments of 300 mg up to a maximum dose of 2,400 mg/day for 6 weeks compared to a placebo arm to analyze an outcome of a decrease in pain intensity, as well as changes in mood and depression in the treatment arm versus the placebo arm. Results showed a statistically significant difference in patient reported pain in the gabapentin arm (p = 0.03, CI = 95%) when compared to the placebo arm, while no changes were noted in mood or depression in the gabapentin arm when compared to the placebo arm. No adverse events were noted throughout the duration of the study. Strengths of the study lie in the design, as the randomization and blinding techniques limited the possibility of bias. Limitations of the study come in the form of a very small effect size limiting the generalizability and validity of the data. Researchers noted larger scale studies are warranted in order to better investigate the effects of gabapentin on mood, sleep interference and activities of daily living.²
In 2001, Huse et al. investigated the effect of morphine in the treatment of PLP in a randomized crossover study lasting four weeks with a one to two week washout period. Pain was measured on a 0-100 VAS comparing the morphine arm of the study to the placebo arm. A total of 12 subjects (10 males versus 2 females) participated in the study with a mean age of 50.58 years and a baseline pain intensity of 4.6/10 using the VAS. The interventions were oral morphine sulfate titrated from 70 mg/day up to 300 mg/day to a maximum tolerable dose for four weeks. Primary outcome was a change in pain intensity as compared to baseline using the VAS. Secondary outcomes included a change in mood and depression as well as quality of life measures via the West Haven Yale Multidimensional Pain Inventory. Results showed a statistically significant decrease in pain in the morphine arm versus the placebo arm ($p = 0.036$, CI = 95%) with about 42% of participants experiencing greater than 50% pain relief. Secondary outcomes failed to show a statistically significant difference in the morphine arm compared to the placebo arm. Reported adverse effects in the morphine arm included tiredness, dizziness, sweating, constipation, vertigo, itching and shortness of breath. This study had significant limitations in terms of design. The sample size was far too small to appropriately interpret the results of this study. More importantly, bias was almost certainly introduced as blinding was not maintained throughout the course of the study. Participants and physicians alike were able to identify the morphine treatment participants due to the observable nature of morphine side effects. Furthermore, the study lasted only four weeks in duration.³

In 2005, Smith et al. investigated the effect of gabapentin in the treatment of PLP in a randomized, double-blinded crossover study lasting six weeks with a five-week
washout period. Randomization was achieved via computer generated randomization techniques. Participants comprised patients with an upper or lower extremity amputation currently experiencing PLP with a minimum of six months status post amputation and an average pain scale of 3/10 using the Numeric Rating Scale (NRS). A total of 24 participants (18 males versus 6 females) were included in the study with a mean age of 52.1 years and a baseline mean pain intensity of 4.3/10. Interventions included gabapentin titrated from 300-3600 mg per day for six weeks. The primary outcome was a mean change in pain intensity in the gabapentin arm when compared to the placebo arm. Secondary outcomes were a mean change in mood and depression as well as changes in quality of life. Results failed to reach statistically significant levels for either the primary or secondary outcome. The study was limited by the significantly underpowered effect size. Strengths of the study stem from the randomization technique as well as the similar baseline characteristics of the participants in terms of pain and location of amputation.4

Current Treatment Options For Phantom Limb Pain

Multiple studies demonstrate current treatments for PLP to be practically ineffective.5 The treatment of PLP is complicated by the complex origin of patient pain, which is estimated to involve both a nociceptive as well as neuropathic component, where neuropathic pain is described as pain in the absence of an external painful (nociceptive) stimulus.6,7 Most researchers consider PLP to be mostly of a neuropathic origin, with treatment recommendations based on known treatments of neuropathic pain syndromes.5 Patients with neuropathic pain are very challenging to manage due to a lack
of evidence-based clinical guidelines alongside the need for individualized therapies. A summary of currently proposed treatments for PLP is found in Table 2.1.

Table 2.1. Proposed Treatments For Phantom Limb Pain5,8

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Pharmacologic Treatments

Anticonvulsants

Gabapentin has shown mixed results with a few randomized controlled trials, some of which demonstrate encouraging results and others failing to show efficacy. These trial sample sizes, however, have been too small to draw appropriate conclusions from.8,10 Pregabalin has been shown to be very safe with the most frequent adverse events noted to be dizziness, somnolence, peripheral edema, headache and dry mouth.9,11,12 To date, there have been no studies investigating the effectiveness of pregabalin as a treatment for PLP.
**Antidepressants**

With their analgesic action attributed to serotonin-norepinephrine blockade combined with sodium channel blockade, tricyclic antidepressants are some of the most commonly prescribed medications for neuropathic pain, including PLP, although study results have been very mixed in terms of their role in PLP treatments. Not only have the study results not demonstrated significant findings, but tricyclic antidepressants have a number of known adverse reactions which include sedation, orthostatic hypotension, aggravation of pre-existing cardiac rhythm disorders, as well as anticholinergic effects such as dryness of the mouth, constipation and urine retention.

**Calcitonin**

The mechanism of action of calcitonin remains unclear in the treatment of PLP with study results yielding mixed results. Clarke et al. has demonstrated a potential benefit of calcitonin treatment if used at the early onset of PLP, but studies conducted outside of the acute onset of PLP symptoms have not demonstrated any benefit from use.

**NMDA Receptor Antagonists**

The mechanism of action of NMDA receptor antagonists in the treatment of PLP is unclear. The use of Memantine has shown some potential benefits in case studies, although randomized controlled trials have not resulted in significant findings.
**Opioids**

Opioids have demonstrated some effectiveness in the treatment of neuropathic pain including PLP.⁹ Comparative trials investigating the benefit of opioids compared to tricyclic antidepressants have shown that while more side effects were noted with opioid treatments, they appear to be just as effective. These studies, however, have not been properly powered.³,⁸. Concern for potential addiction and prescription abuse makes many clinicians reluctant to treat PLP with opioids.⁶

**Non-Pharmacologic Treatments**

*Biofeedback & Complimentary Medicine*

Earlier reports suggest temperature biofeedback may be helpful for the treatment of the burning sensation associated with PLP, but no specific evidence has been demonstrated in clinical trials.⁸ While complementary medicine and biofeedback continues to be widely used in some countries, herbal medicine, acupuncture, muscle relaxation and biofeedback have not been formally assessed in a controlled setting.⁶

*Electroconvulsive Therapy (ECT)*

A case report describing a positive outcome of ECT for the treatment of PLP has been published however the mechanism and role of ECT is not well understood and no formal trials have been conducted at this time.⁸
Mirror Therapy

Ramachandran and Rogers described mirror therapy in 1996 as a potential novel treatment for symptoms related to PLP. Through this therapy, patients insert their intact limb into a box containing a mirror creating the illusion that both limbs are present. Patients are then instructed to move their hands or feet in order to mimic real movement in their missing limb and potentially reproduce cognitive awareness of the missing limb. While certainly an interesting and cost-effective approach to the treatment of PLP, randomized controlled trials have yielded mixed results.

Surgical Intervention

Surgical intervention is traditionally utilized when pharmacologic and non-pharmacologic modalities have failed. Studies resulting in good data investigating the effect of surgical treatment are lacking. Techniques utilized in the past include rhizotomy, cordotomy, thalmotomy and cortical resections. Although there certainly may be a role for surgical intervention in the treatment of intractable PLP, additional studies are required before a conclusion may be reached.

Diabetic Peripheral Neuropathy

Diabetic Peripheral Neuropathy (DPN) is a debilitating and distressing complication of diabetes mellitus that develops in up to 30-50% of diabetic patients. DPN is defined as the presence of symptoms of peripheral nerve dysfunction with symptoms described as burning, electric, sharp, achy and stabbing. In addition to the physical symptoms, neuropathic pain can lead to a negative impact on the quality of life.
of an individual and can have devastating effects on their daily living, mood and sleep.\textsuperscript{14,15} Neuropathic pain can be difficult to treat and can be taxing on both the clinician and the patient as patients rarely experience complete relief of their painful symptoms.\textsuperscript{14,16} Of the many treatment options for DPN, Pregabalin has some of the strongest evidence-based support demonstrating its effectiveness in the treatment of painful symptoms in patients with DPN.\textsuperscript{14,17}

In a 2008 meta-analysis, Hurley et al. examined the effects of pregabalin on painful DPN as it relates to pain control, sleep disturbances and the Patient Global Impression of Change (PGIC) by analyzing data from three different randomized controlled trials with a total of 728 subjects from five different centers. Primary outcome was a change in pain intensity at the conclusion of the study when compared to baseline pain values. Secondary outcomes included the number of patients with greater than a 50\% reduction in mean pain as compared to baseline score as well as PGIC ratings at endpoint as compared to baseline. Results of the meta-analysis showed a significant decrease in pain in the pregabalin arms when compared to the placebo arm (weighted mean difference of 1.15, CI: 95\%). Secondary outcomes also demonstrated favorable results in the pregabalin arm versus the placebo arm. The conclusion of the meta-analysis demonstrated pregabalin to have significant effects on the pain associated with DPN as well as impacting overall quality of life. Strengths of the study lie in the power of the meta-analysis given the large subject size of 728 total subjects. Limitations stem from the overall design of a meta-analysis given the strength of a meta-analysis lies solely on the articles being evaluated. Additionally, pregabalin dosages in each of three randomized controlled trials were not uniform which may have had an effect on the data analysis.\textsuperscript{18}
A 2008 study conducted by Arezzo et al. investigated the efficacy and safety of pregabalin 600 mg/day in the treatment of painful DPN via a double-blind placebo-controlled trial lasting 12 weeks with a week-long dosage escalation period. Pain was measured using the NRS pain scale. A total of 167 subjects participated in the study with 82 in the pregabalin arm and 85 in the placebo arm. In the placebo arm of the study, 45% were male versus 58% in the pregabalin arm and the mean age was 58.2 years with a mean baseline pain intensity of 6.5/10. Primary outcome was a change in pain intensity as compared to baseline using the NRS pain scale. Secondary outcomes included sleep interference and quality of life measurements via the Short-Form McGill Pain Questionnaire (SF-MPQ). Randomization was achieved using a computer-generated random code. Statistical analysis of both the primary and secondary endpoints was achieved using Analysis of covariance (ANCOVA). Results showed a statistically significant decrease in pain in the pregabalin arm versus the placebo arm (p=0.0003, CI: 95%) with 49% of responders experiencing greater than 50% pain relief. Secondary outcomes of a change in sleep interference as well as improvement in quality of life measurements also showed a statistically significant difference in the pregabalin arm compared to the placebo arm (p=0.0019, CI: 95%). Reported adverse effects included peripheral edema and dizziness with peripheral edema being the most common side effect. This was a very well designed study with no apparent limitations. Overall strengths of the study stem from the appropriate effect size as well as strict inclusion and exclusion criteria to attempt to minimize potential confounders.19

A groundbreaking 2004 study conducted by Lesser et al. demonstrated the efficacy of pregabalin in the treatment of painful symptoms related to DPN via a double-
blind placebo-controlled trial lasting five weeks including an initial weeklong titration phase. Subjects were randomized into one of three different dosage arms (75mg/day, 300 mg/day or 600 mg/day) or into the placebo arm. Pain was measured using the NRS pain scale. A total of 338 subjects participated in the study with 77 in the 75mg/day arm, 81 in the 300 mg/day arm, 82 in the 600 mg/day arm and 97 in the placebo arm. Of the 338 subjects, 60% of the participants were male with 95% identifying themselves as Caucasian. The mean age was 60 years of age with a mean baseline pain intensity of 6.4/10. The primary outcome was a change in pain intensity as compared to baseline using the NRS pain scale. Secondary outcomes were daily sleep interference and quality of life assessments utilizing the SF-MPQ and the SF-36 Health Survey. Randomization was achieved via a randomized computer generated code with a block size of eight. Statistical analysis of both the primary and secondary endpoints was achieved using ANCOVA.

Result of the study showed a statistically significant decrease in pain in the 300 mg/day (p=0.0001, CI: 95%) and 600 mg/day (p=0.0001, CI: 95%) pregabalin arms of the study respectively with the 75mg/day arm failing to show a statistically significant difference. Data showed that 46% of the 300mg/day arm and 48% of the 600 mg/day arm achieved a greater than 50% reduction in mean pain scores when compared to baseline. Secondary outcomes analyzing sleep interference and overall quality of life measurements also demonstrated a statistically significant difference in the 300mg/day (p=0.0001, CI: 95%) and 600 mg/day (p=0.0001, CI: 95%). Results of this study demonstrated a dose-response relationship for pregabalin with the 300 mg/day and 600 mg/day arm showing drastic differences in overall pain and quality of life measurements.
when compared to the 75mg/day arm. Reported adverse effects included dizziness and somnolence and peripheral edema with dizziness being the most common side effect. Of interest, side effects were noted much more in the 600 mg/day arm than in the 300 mg/day and 75 mg/day arm. The sample size of the study was a major strength with the Lesser study being the largest DPN double-blind, placebo-controlled trial ever conducted. Additionally, comparing different strengths of pregabalin in a head to head trial made for a very well organized study overall. This study was not without limitations, however. The study duration was only scheduled for five weeks. Ideally, chronic pain studies should be investigated for longer treatment periods with the optimal length being greater than 12 weeks in order to demonstrate durability of the treatment response. Furthermore, generalizability of the study was significantly hindered, as 95% of the study participants were Caucasian.

Post-Herpetic Neuralgia

Post-herpetic neuralgia (PHN) is defined as pain following an acute attack of herpes zoster with similar symptoms as PLP which include burning, lancinating or stabbing pain. Incidence for the development of PHN following an acute attack of herpes zoster ranges from 10-15%. Additionally, more than half of all patients with PHN will experience some form of sleep disturbance along with decreased daily activities as also noted in PLP. Tricyclic anti-depressants and opioid analgesics have been shown to be effective in the management of PHN pain, however, prevalence of side effects and medication addiction is a pressing concern. Pregabalin has been shown to be effective for the management of pain related to PHN in multiple studies.
In a 2003 study, Dworkin et al. looked at the use of pregabalin for the treatment of PHN via a randomized controlled trial. In this study, 173 participants were randomized to either the pregabalin treatment arm (n=89) or the placebo arm (n=84) with the treatment arm receiving 600 mg/day (200 mg every 8 hours) of pregabalin. The primary endpoint was a mean reduction in pain in the pregabalin arm as compared to the placebo arm of the study via the NRS Pain Scale. Secondary endpoints included measurements of sleep interference, quality of life and mood via the SF-36 Health Survey as well as the Profile of Mood States. Study participants were defined as men and women who were at least 18 years of age and had PHN, defined as pain present for three or more months after the healing of a herpes zoster rash. All analysis was performed using the Intent-to-Treat population defined as any patient who received at least one dose of study medication. Primary and secondary analysis was performed via ANCOVA. Results of the study showed 63% of the pregabalin arm versus 25% of the placebo arm reporting reductions in their pain of 30% or more (p=0.001, CI = 95%), which demonstrated a clinically important degree of pain relief. Additionally, 50% of the pregabalin arm versus 20% of the placebo arm reported a 50% decrease in their pain (p<0.005, CI = 95%), which demonstrated a statistically significant difference. Sleep interference scores were also statistically significant in the treatment arm (p=0.0001, CI = 95%) but while the quality of life measurements as assessed by the SF-36 Health Survey did show favorable results in the treatment arm, these results failed to reach significant levels (p=0.051, CI = 95%). The results of this study show pregabalin to be effective in relieving painful symptoms related to PHN and may indicate pregabalin as a treatment option for similar neuropathic pain syndromes.9
While these results are very promising in terms of the use of pregabalin to treat symptoms related to PHN, the study may have introduced potential confounders in that the participants of the study were noted to be 95% Caucasian and were permitted to take opioid and non-opioid analgesics throughout the duration of the study, with as many as 68% of the control arm using some form of these medications at some point during the trial. Additionally, the researchers decided on a pregabalin dose of 600 mg/day (200 mg every 8 hours) although it has previously been shown that while there may be an increased benefit of giving pregabalin at 600mg/day as compared to 300 mg/day for the relief of pain symptoms, adverse effects are dose dependent and noted more frequently in the 600 mg/day cohort.\textsuperscript{21} Strengths of the study lies in the study design as well as the nearly equal distribution of men versus women.

In a 2004 study, Sabatowski et al. set out to investigate the efficacy and safety of pregabalin, and what effect pregabalin had on the reduction of pain, sleep and mood disturbances in patients with post-herpetic neuralgia via a randomized, placebo-controlled clinical trial. In this study, 238 participants were randomized into 3 arms: a pregabalin 150 mg every eight hours arm (n=81), a 300 mg every eight hours arm (n=76) or a placebo arm (n=81) for a total of 8 weeks. The primary endpoint was a mean reduction in pain scores in those receiving 150mg or 300 mg pregabalin when compared to placebo. The secondary endpoints included mean sleep interference scores, quality of life measurements via the Short Form-36 (SF-36) Health Survey Form and depression scores via the Zung Self-Rating Depression Scale.

Efficacy analysis as well as safety analysis was based on the Intent-to-Treat population (ITT population) which was defined as all randomized patients who received
at least one dose of study medication. Primary and secondary analysis was performed via ANCOVA with treatment and clusters, or group of centers, as the fixed effects and the baseline scores as the covariate. Results of the study showed a significantly lower mean pain score for both the pregabalin 150 mg arm (p=0.006, CI = 95%) as well as the pregabalin 300 mg arm (p=0.003, CI = 95%) of the study when compared to placebo. Additionally, subjects in both the 150 mg and 300 mg pregabalin arms of the studies demonstrated significantly reduced weekly mean sleep interference scores as well as improvements in quality of life measurements (p=0.043, CI = 95%) when compared to placebo with efficacy observed as early as week 1 and maintained throughout the course of the study. This confirmed the findings of Dworkin et al. where pregabalin showed a significant decrease in the painful symptoms of PHN (p=0.0001, CI = 95%) as compared to placebo. Based on the results of this study, pregabalin shows promise as a therapy for PHN and may possibly be effective for the treatment of other various neuropathic pain syndromes as well.

While the results of this study were certainly very promising, the design was not without limitations. Sponsors of the study helped with the development and approval processes of the study as well as assisted with the management, biostatistical analysis and provided editorial assistance for the publication. Furthermore, 15 of the 307 subjects screened for inclusion in the study were excluded for “administrative or other reasons”. The sponsor’s participation in various aspects of the study alongside the exclusion of the 15 mentioned subjects without definitive reasoning may all be sources of bias. Additionally, potential confounders can be seen in researcher’s allowance of participants continued use of medications throughout the duration of the study, including opioid and
non-opioid analgesics and antidepressants as well as each of the participants being identified as Caucasian. Strengths of the study lie in the study design itself with a very rigorous definition of what constituted a response, defined as a decrease in mean pain score of at least 50% from baseline to endpoint.\textsuperscript{11}

2.3 Review of the Relevant Methodology

The purpose of this section is to review the methodologies and study designs of previous relevant studies in order to justify the proposed methodology and study design.

\textit{Study Design}

The proposed study will be a randomized controlled trial investigating the effect of pregabalin on the treatment of symptoms related to PLP. The randomized controlled trial study design is a proven hallmark for demonstrating the effectiveness of medications. The intervention will be pregabalin 300 mg/day compared to a placebo arm. Similar to the Sabatowski et al. study, both arms of the study will be permitted to use acetaminophen or ibuprofen for breakthrough pain management as it is unnecessary and perhaps unethical to withhold all forms of analgesic from the placebo arm.\textsuperscript{11,23} The biggest limitation of the Lesser trial is that it was shorter in duration than would normally be ideal for chronic pain studies.\textsuperscript{20,21} The proposed study will be similar to the Arezzo et al. study, which lasted 12 weeks in order to demonstrate durability of the treatment response.\textsuperscript{19}
RFID

Poor adherence to medication compliance has been a consistent barrier to clinicians achieving better clinical outcomes for their patients.\textsuperscript{24} This same barrier holds true for clinical researchers relying on study participants to take their medications as directed. Studies have demonstrated that as many as 50\% of all patients do not adhere to their prescription medication regimen.\textsuperscript{24} One novel approach that may solve this compliance dilemma is through the use of RFID technology.\textsuperscript{25} Mediary Corporation, located in Ontario, Canada, has invented a RFID compliance monitoring system that embeds RFID tags into the prescription blister packaging to allow for direct electronic monitoring of the date and time a patient or research participant opens a medication package.\textsuperscript{25,26} This technology allows the investigation team to scan the used packaging where a subsequent usage pattern can then be plotted and analyzed for compliance.\textsuperscript{25} The plotted data would not only aid the research team in verifying compliance, but also would be beneficial for validating side effect complaints by analyzing the time dosages were taken and comparing this to self-reported adverse effects. Furthermore, the RFID technology also has the capability to alert a patient or research participant to take their medication when due via text message or by simply calling the patient with an automated reminder.\textsuperscript{26}

Patient Selection

Similar to the study by Jensen et al., participants from this study will be recruited from various Department of Veteran Affairs (VA) Hospitals.\textsuperscript{27} The VA hospital system is not only home to one of the oldest electronic medical record (EMR) systems in the
country, but through a joint effort between the Department of Defense and Department of Veteran Affairs, all Iraq and Afghanistan related traumatic amputations are closely tracked by Walter Reed Army Medical Center in Washington, D.C. allowing for a larger pool of potential study participants."Strict inclusion and exclusion criteria will be enforced in order to minimize confounders. Inclusion criteria will include: timeline of six months or greater since amputation from the start of the study^4, confirmation of neuropathic pain via a score of 12 or greater on the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)^15, average daily pain of 4/10 or greater^11,19 and female subjects will be required to be non-pregnant and non-lactating^9,11. Subjects presenting with any of other cause of painful neuropathy to include B12 deficiency, hypothyroidism, uremia or diabetic peripheral neuropathy^14,17 and subjects whose Creatinine clearance rates are ≤ 60 mL/min using the Cockcroft-Gault equation will be excluded from the study^19,21.

**LANSS Pain Scale**

Interested participants will initially be screened to verify the source of pain as neuropathic in origin versus that of nociceptive or psychogenic via the LANSS pain scale. The LANSS pain scale is a screening tool designed to aid clinicians and researchers in distinguishing neuropathic pain from pain of a different origin.\(^{28,29}\). This tool consists of a total of 7 items: a 5-item questionnaire to determine pain symptoms as well as 2 items that involve a clinician administered test to evaluate for the presence of a decreased sensation to pin prick as well as allodynia, or a pain response from a stimulus which would normally not provoke a painful response.\(^{29}\) The binary responses of ‘yes’ or
‘no’ are each weighted differently depending on the odds ratio of a positive response as predictive of pain as neuropathic in origin. The responses are then tallied with possible scores ranging from 0 to 24 with a score of 12 or more considered suggestive of pain as neuropathic in origin.\textsuperscript{15,30} Sensitivity for the LANSS Pain Scale ranges from 74-78% along with a specificity of 80%.\textsuperscript{28,30} The internal consistency and validity of the LANSS has been tested in a number of different settings and has been confirmed to be a valid and reliable instrument for distinguishing pain of neuropathic origin.\textsuperscript{28}

\textit{Intervention}

\textbf{Pregabalin}

Pregabalin is an alpha\textsubscript{2}-delta ligand with analgesic, anxiolytic, and anticonvulsant properties.\textsuperscript{9,11,12} Potent binding at the alpha\textsubscript{2}-delta receptors reduces calcium influx at nerve terminals which in turn decreases the release of several neurotransmitters responsible for pain transmission like glutamate, noradrenaline and substance P with the analgesic effects being two to four times more potent than gabapentin in the treatment of neuropathic pain with remarkable safety and efficacy.\textsuperscript{12,31} Other known benefits of pregabalin include improvements in both sleep disturbances and anxiety, and a very mild side effect profile which includes dizziness, somnolence, headache, dry mouth, peripheral edema, weight gain and blurred vision.\textsuperscript{13} The only known contraindication to pregabalin is renal insufficiency.\textsuperscript{12} The dosage of pregabalin was adopted from the Dworkin et al. and Lesser et al. studies which both showed a dose of 300 mg/day with an appropriate titration to be an effective treatment option for DPN with little to no side effects noted.\textsuperscript{9,21}
Primary Outcome Measures

NRS Pain Scale

Pain intensity and severity are the single most frequently assessed variables in clinical research investigating pain treatment. The primary outcome of the proposed study will be a mean change from baseline in patient reported pain as measured via the NRS pain scale. This primary outcome was chosen based on a number of prior studies investigating potential treatments for symptoms related to the treatment of painful neuropathy. The NRS is a pain scale designed to measure pain intensity where 0 = no pain and 10 = the worst possible pain imaginable and is widely used to assess pain. Pain scales such as the NRS have been deemed psychometrically sound and are easily interpreted by patients and clinicians alike. Additionally, the NRS is often considered a first-line pain severity scale when sensitive and responsive measures of pain intensity are required. For these reasons, the NRS has been widely used in the evaluation of pain severity in both clinical and research settings.

It is not only necessary to assess the level of pain experienced but to also stratify pain into “mild”, “moderate” and “severe” categories based on the impact pain has on quality of life. Through multiple post hoc analysis of placebo-controlled trials, cut points have been established as “mild” being 1-3, “moderate” being 4-6 and “severe” being 7-10 based on symptom similarities within the three groups with pain beginning to have a serious impact on functioning and quality of life when it reaches a level of 5 out of 10. A reduction in pain of two points from baseline has been shown to be statistically significant.
In a 2010 study, Hoffman et al. attempted to investigate how changes in pain severity levels corresponded to changes in health status and function in patients with painful diabetic peripheral neuropathy via a post hoc analysis of a 12-week, multi-national, placebo-controlled trial of pregabalin for the treatment of diabetic peripheral neuropathy. In this study, 401 patients were analyzed in order to establish NRS cut-points as well as describe the relationship between changes in pain levels and what effect this change has in function and health status. Investigators in this study sought to establish the level of improvement in pain necessary to demonstrate a statistically significant difference as well as to establish what clinical meaningfulness could be extrapolated from this data. The results indicated the cut-points established by previous studies were consistent when compared to different health related measures. These findings served to provide evidence of convergent validity as well as to help confirm NRS pain scales as a well-validated tool for establishing pain severity. When changes in pain levels were compared to changes in quality of life metrics, the results suggest that patients whose pain was not reduced to a “mild” level of severity were still experiencing clinically important changes in function and health status even when those changes were not considered statistically significant. As one might expect, patients with higher levels of pain severity reported a much greater decrease in overall health status, sleep, daily functioning and an increase in depression. 

A great deal of evidence supports NRS pain scales as being both valid and reliable when attempting to measure pain intensity across a number of different patient populations suffering from a multitude of pain disorders which include back pain, carpal tunnel syndrome, osteoarthritis and PLP. Furthermore, the NRS pain scale is the
primary basis for the World Health Organization’s (WHO) analgesic ladder with an emphasis on differentiating pain severity into “mild”, “moderate” and “severe” categories.

Secondary Outcome Measures

SF-36 Health Survey

Secondary outcomes of the proposed study will be changes in quality of life as assessed by the SF-36 Health Survey. The SF-36 is a self-administered questionnaire that contains 36 items, takes approximately five minutes to complete and has been used as an outcome measurement instrument to assess quality of life in amputees. The SF-36 evaluates eight aspects of general health to include: 1.) Physical functioning, 2.) Body pain, 3.) Role limitations due to physical health problems, 4.) Role limitations due to personal or emotional problems, 5.) General mental health, 6.) Social functioning, 7.) Energy, and 8.) General health perceptions. The maximum score in each section is 100 with higher scores demonstrating a higher quality of life. An increase or decrease of 5 units has been shown to be clinically relevant. Numerous studies investigating potential treatments for symptoms related to painful neuropathy have included quality of life measurements as a secondary outcome.

In a 1992 study, Brazier et al. sought to test the acceptability, validity and reliability of the SF-36 health survey questionnaire form using 1,980 patients who varied in age from 16-74 years old. Brazier et al. wanted to identify a questionnaire that was brief, easy to use and preferably self-administered. Overall, the data showed a response
rate of 83% and the rate of completion for each dimension was greater than 95%.

Additionally, the SF-36 was able to detect very low levels of ill health in patients who had previously been deemed to be in good health per the screening of alternative quality of life assessment forms. The researchers concluded the SF-36 Health Survey Form was easy to use, acceptable to the patients and fulfilled very strict criteria of both test-retest reliability as well as validity and proclaimed the SF-36 to be a promising instrument for measuring overall health perception. Overall, the SF-36 is a reliable tool for assessing quality of life metrics in an amputation population with a specificity of 92% and a sensitivity of 71%.^41,45

**Change In NRS Pain Scale Cut-Off Levels**

While a reduction in pain of two points on a 10 point scale from baseline on the NRS Pain Scale has been shown to be statistically significant, changes in NRS Pain Scale cut-off levels are important indicators to measure the extent to which a particular treatment if effective at reducing pain either from “severe to moderate” or “moderate to mild”.^27,37,38 Furthermore, changes in pain scale cut-off levels serves as a measure of a clinically important difference. These changes in pain scale cut-off levels may in fact demonstrate the patient-care implications of clinical research study results.^27,37

**Sample Size**

With many of the trials for the treatment of PLP using small study sizes, a demonstrated need for additional studies is apparent with an emphasis on appropriate
effect sizes.\textsuperscript{10} Most studies have been short-term assessments of vastly underpowered studies, which directly inhibits the detection of significant differences between groups.\textsuperscript{5} Estimating the sample size from appropriately powered neuropathic pain trials is crucial for yielding useful data (see Table 2.2 Summary of Published Clinical Trials Sample Size Data).\textsuperscript{11} Furthermore, attrition estimates are important for pain trials given the higher than average dropout rates experienced.\textsuperscript{20} Studies of a similar design as this one have experienced a 20-25\% attrition rate.\textsuperscript{11,15}

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DIFFERENCE IN PAIN (MEAN CHANGE)</th>
<th>POWER</th>
<th>STANDARD DEVIATION</th>
<th>LEVEL OF SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROSENSTOCK, 2004</td>
<td>1.26</td>
<td>90%</td>
<td>2.12</td>
<td>0.05</td>
</tr>
<tr>
<td>LESSER, 2004</td>
<td>1.3</td>
<td>90%</td>
<td>2.5</td>
<td>0.05</td>
</tr>
<tr>
<td>FREYNHAGEN, 2005</td>
<td>1.26</td>
<td>95%</td>
<td>2.12</td>
<td>0.05</td>
</tr>
<tr>
<td>SABATOWSKI, 2004</td>
<td>1.3</td>
<td>90%</td>
<td>2.5</td>
<td>0.05</td>
</tr>
<tr>
<td>DWORKIN, 2003</td>
<td>1.3</td>
<td>90%</td>
<td>2.35</td>
<td>0.05</td>
</tr>
</tbody>
</table>

2.4 Conclusion

Several studies have shown pregabalin to be effective in the treatment of painful neuropathic symptoms such as DPN and PHN.\textsuperscript{9,11,12,18,19,21} To date, there have been no studies performed investigating the effect of pregabalin in the treatment of symptoms related to PLP. Randomized controlled trials with adequate sample sizes are needed to investigate a potential treatment option for such a devastating disease as PLP.\textsuperscript{5}
References


34. Freynhagen R, Strojek K, Griesing T, Whalen E, Balkenohl M. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind,


Chapter Three: Study Methods

3.1 Study Design

This study aims to conduct a multi-centered, double blinded, placebo-controlled, 15-week randomized controlled trial to evaluate the effect of pregabalin in patients who experience PLP, defined as a painful sensation in an amputated limb.

3.2 Study Population and Sampling

For my methods, we intend to use a stratified sampling of United States Veterans of military service who have had a previous amputation and are currently experiencing symptoms related to PLP. The recruitment period will last a total of 16 months. Inclusion criteria will consist of greater than six months time between time of amputation and start of the study, confirmation of neuropathic pain via a score of 12 or greater on the LANSS, and average daily pain of 4/10 or greater. Female subjects must be non-pregnant and non-lactating. Exclusion criteria will consist of: subjects with any other form of painful neuropathy (B12 deficiency, hypothyroidism, uremia, diabetic peripheral neuropathy, etc.) or subjects with a creatinine clearance rate ≤ 60 mL/min using the Cockcroft-Gault equation. Inclusion criteria will be reviewed by a board-certified neurologist prior to randomization. Baseline laboratory tests obtained prior to the start of the study will include a hematological panel (hemoglobin, hematocrit, complete blood cell count (CBC), chemistry panel (AST, ALT, BUN, Creatinine, glucose, potassium) and a urinalysis.

Baseline characteristics will be analyzed to account for any potential confounders not omitted via the inclusion and exclusion criteria. These characteristics include: age,
gender, race, initial level of pain, duration and location of symptoms, BMI, blood pressure and laboratory results (see Table 3.1 Clinical Characteristics).

Table 3.1. Clinical Characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>18-50</th>
<th>51-60</th>
<th>61-70</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Non-Hispanic White</td>
<td>Non-Hispanic Black</td>
<td>Mexican American</td>
<td>Other race/ethnic groups</td>
</tr>
<tr>
<td>Initial Level Of Pain</td>
<td>4-6 (Moderate)</td>
<td>7-10 (Severe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of Symptoms (years)</td>
<td>≥1 year</td>
<td>1-2 years</td>
<td>3-5 years</td>
<td>5+ years</td>
</tr>
<tr>
<td>Anatomic Location of Amputation</td>
<td>Upper Limb</td>
<td>Lower Limb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>&lt;18.5</td>
<td>18.5-24.9</td>
<td>25-29.9</td>
<td>≥30</td>
</tr>
<tr>
<td>Blood Pressure (mm Hg)</td>
<td>&lt;140/90</td>
<td>≥140/90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lab Results at Baseline</td>
<td>CBC</td>
<td>LFT</td>
<td>Hemoglobin A1c</td>
<td>Urinalysis</td>
</tr>
</tbody>
</table>

3.3 Participant Protection and Confidentiality

Prior to the start date, the Yale University Human Investigation Committee will approve all parameters of the study. Additionally, there will be a strict adherence to all documentation required by the Yale Human Research Protection Program including an Informed Consent Form, which explicitly lists the details of the study as well as describes any inherent risks associated with the use of pregabalin treatment in an easily understood language format [Appendix B]. A copy of the Informed Consent Form will be made available to all participants at the time of signing.

All members of the investigation team will be required to have up-to-date Health Insurance Portability and Accountability Act (HIPAA) training as well as provide proof of training prior to the start of the study. All participants will sign a Privacy Rule
Authorization Form that outlines the participants understanding of their consent to share health information as well as medical record information with the investigation team [Appendix C]. Printed copies of the Privacy Rule Authorization Form as well as a copy of the Patient’s Bill of Rights will be provided to the participant prior to the start of the study in keeping with the Health Insurance Portability and Accountability Act of 1996.

Any and all information obtained throughout the course of the study will be password protected on a computer specifically designated for the study. Access will only be granted to members of the research team who are required to utilize the information for study purposes. Individual user ID’s and passwords will be required for each member of the investigation team who requires access to the patient information in accordance with Yale University Information Technology Services policies and procedures.

Participants of the study will receive a unique patient identifier at the start of the study to maintain the double-blind status of the study as well as protect the participants’ identity. All identifying information will be destroyed upon completion of the study.

There are no serious risks anticipated with participating in this study. All participants will be made aware of all known side effects of pregabalin prior to the start date of the study. Participants will be required to meet face-to-face with an affiliated board-certified neurologist throughout the course of the study. The neurologist will evaluate any and all concerning symptoms or side effects that may be experienced from the pregabalin treatment (see Table 3.2 Summary of Clinical Visits). Additionally, participants may reach a member of the investigation team at any time if they develop any symptoms or side effects throughout the duration of the study.
Table 3.2. Summary of Clinical Visits

<table>
<thead>
<tr>
<th></th>
<th>BASELINE</th>
<th>WEEK 5</th>
<th>WEEK 10</th>
<th>WEEK 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full Neurological</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Exam</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Diary</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>LANSS</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Labs</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Creatinine Clearance</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess for Adverse</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Effects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.4 Recruitment

Participants for this study will be recruited from various Department of Veteran Affairs hospitals throughout the United States. Recruitment will be achieved through a coordinated effort through the Department of Veterans Affairs with the study relying heavily on clinician referrals of likely study candidates, as well as strategic placement of recruitment flyers throughout Veteran Affairs hospitals [Appendix A].

All potential study participants will be informed that the goal of this 15-week study is to evaluate the effect of pregabalin in symptoms related to PLP in post-amputation patients. Participants will be made aware their involvement in this study could provide the necessary evidence to better assist clinicians in the treatment of PLP as no gold-standard treatment currently exists. Likewise, they will be made familiar with the study design detailed in the Informed Consent Form, which includes the baseline history and physical, required lab work prior to the start of the study to prevent confounding as well as to ensure patient safety, as well as the necessity of providing a weekly pain score to the investigation team [Appendix B]. Informed Consent Forms will explicitly state that all participants may withdraw from the study at any time. Lastly, participants in the study will be informed they will receive all medications, forms associated with the study,
laboratory testing and ongoing medical examinations free of charge for the duration of the study, however no additional compensation will be provided to the participant at any time.

3.5 Randomization and Assignment of Intervention

Following the initial week-long baseline phase, all participants will be randomized via a simple randomization technique using computer generated random numbers into either the pregabalin interventional arm or the placebo control arm for the 15 week duration of the study. All members of the research team as well as the study participants will be blinded to the group assignments until the conclusion of the study. Active drug and placebo will be randomized and marked via identification numbers to maintain the integrity of the double-blinded status of the study.

3.6 Adherence and Adverse Effects

Participants in each arm of the study will provide weekly updates of their pain status via an automated IVR System. Additionally, study participants will be required to complete a week-long compliance assessment during which they will report their pain levels for one week awhile taking a placebo. Compliance will be monitored via RFID technology and study subjects will be asked to return their medication packaging at the end of the compliance assessment and routinely throughout the study to monitor ongoing compliance. The participants will also fill out a health survey form during the baseline week and again at the completion of the study in order to monitor any changes in quality of life factors.
Study participants will have face-to-face visits with a board-certified neurologist periodically throughout the study. Those visits will be scheduled during the baseline compliance week, week 5 and week 10, with a final visit to occur during the last week of the study. Neurologists will be blinded to whether the participant has been randomized to the pregabalin arm or the placebo arm of the study. Serious adverse effects are not anticipated as the Food and Drug Administration has approved pregabalin for the treatment of similar symptoms diabetic neuropathies. However, in the event that a participant experiences an adverse reaction, the participant will be instructed to notify the investigation team. A neurologist will review the symptoms with the study participant and decide whether they should continue with the study. If the experienced side effects are intolerable or deemed dangerous by the neurology team, the study participant will be removed from the study. The participant will fill out end-of-study questionnaires at the time of removal from the study.

3.7 Study Variables, Measures and Data Collection

The independent variable will be an oral dose of pregabalin of 300 mg/day (100 mg every 8 hours) with an initial week-long titration phase and a week-long taper phase during the final week of the study (see Figure 3.1 Pregabalin Dosage Titration Schedule and Table 3.3 Pregabalin Dosage Schedule For Week-14 Taper).
The control will be the placebo medication receiving placebo medication that identical to the active drug. The primary dependent variable is the mean change in pain from baseline in the treatment arm as compared to the placebo arm. The secondary dependent variable is improvement in quality of life measurements in the treatment arm as compared to the placebo arm. Both arms of the study will be permitted to use acetaminophen and NSAID’s as needed for breakthrough pain. Use of rescue pain medication will be logged via the IVR System and analyzed post hoc.

Pain will be logged daily beginning with the baseline compliance week and continuing until the completion of the study at the end of week 15. Study participants will be asked to record their pain on a pain scale [Appendix D] and log their pain into a pain diary [Appendix G]. Participants will report their daily pain scale scores via an automated
(IVR) System. Mean weekly pain scores will be calculated and compared in order to assess what effect pregabalin has on overall pain. Labs to be collected during the baseline visit as well as the final visit will include a CBC, LFT, Hemoglobin A1c and a urine sample for a routine urinalysis. Data and information obtained during all face-to-face visits as well as lab results will not be made available to the investigation team until after the completion of the study. To measure participant compliance in respect to taking the study medication, RFID technology will be incorporated, and the data will be graphically plotted for analysis. To measure the primary outcome, a NRS tool for self-reporting of Pain will be logged at baseline as well as daily during the duration of the study [Appendix D]. To measure the secondary outcomes, a SF-36 Health Survey will be completed at baseline as well as at the completion of the study [Appendix F].

3.8 Sample Size

To successfully complete this study, it is estimated a total of 142 participants will be required (71 participants assigned to each arm of the study) in order to detect a mean change in patient-reported pain of 1.3 from baseline using the NRS Pain Scale. This statistically significant difference was established using similar pain studies as well as literature validating the accuracy of the NRS Pain Scale. In order to estimate the sample size, a T test calculator (Power and Precision version 4. 2000 Biostat, Inc. Engelwood, NJ.) was used to compare two independent means for a two-sided alpha of 0.05 and a power of 80%. Additionally, the sample size of 142 participants also takes into account an attrition rate of 20% to correct for potential dropouts during the course of the study [Appendix H].
3.9 Analysis

All data collected throughout the duration of this study will be analyzed using Statistical Analysis software. In order to reduce confounders, baseline characteristics for descriptive statistics will be stratified according to: age, gender, race, duration of symptoms, initial level of pain, anatomic location of the amputation, body mass index and blood pressure. In order to assess the primary and secondary outcomes, the participants will fill out various forms including: the LANSS Pain Scale [Appendix E], SF-36 Health Survey [Appendix F], NRS Tool for Self Reporting Pain [Appendix D] and Pain Diary [Appendix G]. All analysis will be carried out utilizing the Intent-to-Treat population, defined as any patient who received at least one dose of study medication. Primary analysis of the data will be conducted using ANCOVA with treatment and cluster, or group of centers, as fixed effects and baseline scores as the covariate adjusting for the use of concomitant medications, which include NSAIDs and acetaminophen. Secondary analysis of the data will be conducted using Linear Regression adjusting for baseline pain. Adverse effects will be analyzed using Fisher’s exact test.

3.10 Timeline and Resources

A total of 21 months will be required for the completion of this study. 16 months will be dedicated solely to participant recruitment. Following the recruitment phase, there will be a one week baseline and compliance phase, one week for the dose escalation phase, 12 weeks for the dose stability phase, and one week of the dose taper phase for a total intervention time of 15 weeks. The remaining five weeks will be dedicated to compiling data as well as statistical analysis.
Study headquarters will be housed at the Department of Neurology at the West Haven Veteran Affairs Hospital located at 950 Campbell Ave, West Haven, CT. Study personnel will include the student primary investigator, Brandon Beattie, PA-SII as well as the thesis advisor and primary investigator, Huned Patwa, MD. A team of board-certified neurologists will be required in order to conduct baseline history and physicals as well monitor participants throughout the course of the study for any potential adverse effects to the medication. A phlebotomist will be required for initial baseline laboratory draws as well as end-of-study laboratory draws. A dedicated research assistant will be necessary in order to assist the investigation team with patient consents as well as data consolidation and analysis. A statistician will be needed at the conclusion of the interventional time to assist with statistical analysis of the data.

Required resources include the pregabalin medication as well as placebo medication in the form of a sugar pill identical to the shape and color of the pregabalin as well as over-the-counter strength acetaminophen and NSAIDs for concomitant analgesic use in both the control arm and placebo arm of the study. This is an imperative detail necessary to maintain the double-blinded status of the study in order to minimize bias. Pregabalin dosages of both 25 milligram (mg) and 50 milligram (mg) pills are necessary in order to successfully complete the titration phase and dose-taper phase of the intervention period. Equipment needed for the study includes a dedicated phone line, a workspace with computer access, a RFID enabled smartphones and RFID labels as well as an automated IVR System through which study participants to record their weekly pain scale results and total number of medication doses taken during the day.
Chapter Four: Conclusion

4.1 Advantages and Strengths

Overall, this study has several strengths. Strict inclusion and exclusion criteria will be utilized as well as an analysis of baseline characteristics in an effort to minimize possible confounders. Additionally, the study will be utilizing pain scales and quality of life metrics that have been well validated in previous studies.\textsuperscript{1-5} Another strength of the study is the chosen timeline. Ko et al. have shown the appropriate study duration for investigating chronic pain should be 12 weeks or greater in order to verify durability of the desired response.\textsuperscript{4} Lesser et al. were able to show a statistically significant difference in pain with the treatment of pregabalin but the study only lasted five weeks. This study is scheduled to last a total of 15 weeks (one week for the dose escalation phase, 12 weeks for the dose stability phase and a final week for the dose taper phase). Strength of this proposed study also comes in the form of the choice to pool subjects from U.S. Department of Veteran Affairs hospitals. VA hospitals utilize a comprehensive standardized electronic medical record system allowing for relatively easy access to a large patient population thereby minimizing potential research obstacles.

4.2 Disadvantages and Limitations

While great strides were made to formulate a comprehensive study design, this study is not without potential limitations. As no biomarker or gold standard for diagnosing PLP exists, there is a possibility of including subjects into the study who are experiencing pain from sources other than PLP. This study only utilizes one dosage of pregabalin in the control arm rather than investigating the possible effect multiple
dosages may have on the treatment of symptoms related to PLP. Future studies may wish to further stratify the control arm into cohorts who are given multiple dosages of pregabalin. Additionally, this study utilized a single treatment modality rather than a multiple treatment modality. Future studies may wish to focus on what effect, if any, a combination regimen of pregabalin alongside medications such as tramadol or acetaminophen may have in respect to a better potential therapeutic response versus the use of a single agent alone.\textsuperscript{4,6,7}

Furthermore, the source of patient sampling may pose a possible issue in terms of the generalizability of the study results. While recruiting patients from the Department of Veteran Affairs certainly has advantages, one potential setback is the potential risk of decreasing the generalizability of the results given the unique characteristics of a veteran population. Lastly, while this study did incorporate tools for assessing overall quality of life through the use of the SF-36 Health Survey Form, there was no emphasis on what effect, if any, sleep disturbances may have on overall quality and severity of PLP. Sleep disturbances have been shown to have a direct effect on pain.\textsuperscript{8} Future studies may wish to incorporate a baseline polysomnography (PSG) sleep study and compare these results to end-of-study PSG results to further elicit what effect sleep disturbances have on PLP.\textsuperscript{8}

### 4.3 Clinical Implications

PLP is a devastating pain syndrome affecting up to 80% of all post-amputation patients with no clear gold standard of treatment.\textsuperscript{7,9} By 2050, an estimated 3.6 million Americans will have an amputation as a result of either trauma, medical complications or disease progression.\textsuperscript{7} Given this estimate, a need clearly exists for well designed trials investigating potential treatment options for PLP. Pregabalin is proven to be effective for
the treatment of painful neuropathic symptoms in syndromes such as DPN and PHN and may have the potential to be a useful treatment option for PLP.\textsuperscript{5,10,11} If proven effective, implications of pregabalin as a treatment regimen for PLP could significantly reduce painful symptoms, be a cost effective option and vastly improve the quality of life of individuals suffering from PLP.\textsuperscript{12} Results of this study may also provide substantial evidence to better assist the U.S. Department of Veterans Affairs in standardizing the treatment of PLP in veterans experiencing PLP who have either lost a limb as a direct result of military conflict or in patients undergoing surgical amputations.
References


Appendix A: Recruitment Flyer

Do you suffer from pain in an amputated limb?

We are looking for individuals who experience pain in an amputated limb to participate in an upcoming research study. Please contact me if you’re interested or have any questions!
Appendix B: Informed Consent Form

This Informed Consent Form is for men and women who have had an upper or lower limb amputation via either traumatic or surgical removal and experience symptoms related to Phantom Limb Pain who are invited to participate in a research study. This study aims to research what effects pregabalin may have in decreasing pain and discomfort associated with Phantom Limb Pain.

Name of Principal Investigator: Brandon Beattie, PA-SII and Huned Patwa, MD
Name of Organization: Yale University Physician Associate Program
Name of Proposal: The Effect of Pregabalin in Patients With Phantom Limb Pain: A Randomized Controlled Trial

This Informed Consent Form has two parts:
- Information Sheet (to share information about the research with you)
- Certificate of Consent (for signatures if you agree to take part)

You will be given a copy of the Informed Consent Form in its entirety

PART I: Information Sheet

Introduction
I am Brandon Beattie, a Yale University Physician Associate student. I aim to research possible treatment options for Phantom Limb Pain, a devastating syndrome effecting up to 80% of individuals who have had an arm or leg amputation. Here you may find information related to the study in order to better assist you with deciding if you would like to participate in the research. You do not have to decide today whether or not you would like to participate.

If you do not understand any words or descriptions related to the study, please ask for clarification and someone from the research team will take the time to explain them as clearly as possible to you. If you have any questions or concerns at a later date and time, you may direct them to any of the research team members.

Purpose of the research
Phantom Limb Pain is defined as pain in a region of the body that has been removed due to amputation and is very commonly experienced after an amputation of an upper or lower limb. The treatment options currently used to help people suffering from Phantom Limb Pain do not appear to be very effective with helping patients to manage their ongoing pain.
and decreased quality of life. There is a medication, pregabalin, that has been studied extensively in the diabetic population for the treatment of neuropathic pain (pain originating from the nerves). We believe pregabalin may help with the treatment of pain related to Phantom Limb Pain in amputation patients as well, however the use of pregabalin for the treatment of symptoms related to Phantom Limb Pain has not been previously studied. The reason we are doing this research is to determine if pregabalin is effective in the treatment of pain and discomfort associated with Phantom Limb Pain.

**Type of Research Intervention**
This research will involve taking a pill three times a day as well as asking you to document your pain using a form that will be provided to you. The pill may be the medication pregabalin or it may be a placebo in which case no active drug will be administered. You will be randomly assigned to either the medication group or the placebo group and neither you nor the research team will be made aware of whether you have been assigned to the medication group or placebo group until after the 15-week trial has finished.

**Participant selection**
We are inviting all adults who have had an amputation of an upper or lower limb and who meet all of the inclusion criteria parameters to participate in research to determine if the drug, pregabalin, is effective in the treatment of pain and quality of life in individuals suffering from symptoms related to Phantom Limb Pain.

**Voluntary Participation**
Your participation in this research study is completely voluntary. All healthcare services you receive from your clinicians will continue during the duration of the study. If you choose not to participate in this research study, you will continue to be offered treatment options routinely used in the treatment of your symptoms. You may opt to remove yourself from the study at any time.

**Information on the Trial Drug**
The drug we are testing in this research is called pregabalin. It has been tested extensively before in people who do not have symptoms related to Phantom Limb Pain but who experience nerve pain related to worsening diabetic complications. We now want to test the medication on people who have pain and decreased quality of life due to Phantom Limb Pain. This is called a “phase 2” trial.

You should know that pregabalin has a few known side effects. Side effects of pregabalin include unusual tiredness or weakness, dizziness, angioedema or peripheral edema (swelling of the face, mouth, or extremities), hypersensitivity, suicidal behavior, and weight gain. Less common side effects include labored breathing and shortness of breath. As your body adjusts to the medication, these side effects may go away in the event you do experience them. We know of no other problems or risks associated with the use of pregabalin.

Some participants of this research study will not be given the drug pregabalin. Instead, they will be given a placebo pill that contains no active medication. This is to better understand
the effects pregabalin may have on treating the symptoms related to Phantom Limb Pain. If you decide to participate in this research study, you will be randomly assigned to either the pregabalin group or the placebo group. During the duration of the 15-week study, neither you nor members of the research team will know which group you have been assigned to. There is no known risk associated with the placebo pill.

Procedures and Protocol
A. Unfamiliar Procedures
For this study, we need to compare two groups of people who experience Phantom Limb Pain: one group who will receive the medication pregabalin and another group who will receive a placebo. A placebo is an inactive medication that looks identical to the real medication. This is so the research team nor the participant are aware if they are taking the actual medication or the placebo in order to best decide how well a medication works for a particular illness or symptom relief. Over-the-counter strength acetaminophen and NSAIDs will be permitted throughout the duration of the study.

The groups will be selected at random. It is important that neither you, as the participant, nor your research team know which group you have been placed in so that the results will not be influenced unintentionally. The two groups will then be compared at the end of the trial. Healthcare workers will be monitoring you and the other participants very carefully throughout the course of this study. If you have any concerns or worries during the course of the study, please bring these up either to myself or any member of the research team.

B. Description of the Process
During the first visit, you will be asked to answer a series of easy to understand questionnaires in order to establish what your baseline pain and quality of life is. Following the initial visit, we will then ask you to track your daily pain for a total of 7 days while taking a sugar pill as well as calling a toll-free number to record your daily pain scale. This is to verify your willingness to comply with the research study process.

During the next week, we will begin a week-long period of dose escalation. You will be asked to take one (1) 50 mg tablet three (3) times a day for one week. You will also be asked to log your pain in a daily log that will be provided to you as well as record your weekly pain scale via telephone.

Following the dose escalation period, you will be asked to take one (1) 100 mg tablet three (3) times a day for 12 weeks. During this period, you will be asked to continue to log your pain in a daily log that will be provided to you as well as record your weekly pain scale via the telephone. Compliance in respect to taking the medication as directed will be monitored via radiofrequency identification (RFID) technology within the medication packaging.

The last week of the study will consist of a 1-week tapering period where you will gradually be reducing your dose as directed in order to minimize any adverse effects of discontinuing the drug abruptly to include insomnia, nausea, headache, anxiety, diarrhea, and excessive sweating.
Duration
This research study is scheduled to last a total of 15 weeks. During that time, it will be necessary for you to meet with the research team periodically. We will do our best to conduct most of our interviews over the phone, face-to-face meetings are important during the initial week and necessary occasionally throughout the course of the study in order to insure your safety as well as the integrity of the study.

Side Effects
As previously mentioned, the medication pregabalin may have some unwanted side effects. This may include unusual tiredness or weakness, dizziness, angioedema or peripheral edema (swelling of the face, mouth, or extremities), hypersensitivity, suicidal behavior, and weight gain. Less common side effects include labored breathing and shortness of breath. The research team will monitor you closely throughout the course of the trial and keep track of any unwanted side effects or problems.

Risks
Pregabalin has been approved by the U.S. Food and Drug Administration for use in patients experiencing diabetic neuropathy and researched extensively in the diabetic community. With that said, there is always the potential for harm when introducing a new medication to your body. We will do everything we can to decrease the likelihood of any adverse events.

Benefits
With your participation in this research study, you will be provided all medications free of charge. Additionally, you will be compensated for any travel expenses you incur during the few times the research team must meet with you in person throughout the course of the study. You may not experience any personal benefits from participating in this study, however your participation is crucial in order to help investigate if pregabalin is helpful in the treatment of pain and a decreased quality of life due to symptoms related to Phantom Limb Pain.

Confidentiality
Throughout the course of this study and afterward, your confidentiality is of the utmost importance to your research team. Any information collected from you will be marked with an identification number rather than your name or personal information. Only the research team will know the names of the participants in this study. Names or personal information will never be published or released.

Right to Refuse or Withdraw
You do not have to participate in this research study if you do not wish to do so. You may also remove yourself from the study at any point during the 15-week period if you wish to do so. Please contact a member of the research team if at any point you decide you no longer wish to participate in the research study.

Point of Contact
If you have any questions or concerns, you may contact me at any time. I may be reached via email at brandon.beattie@yale.edu or you may write to me at:
This proposal has been reviewed and approved by the Yale University Physician Associate Program Thesis Committee, Yale University Institutional Review Board (IRB) and Human Investigation Committee (HIC) whose tasks are to make sure that research participants are protected from harm or unnecessary risk.

PART II: Certificate of Consent

I have read the foregoing information, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research study.

Name of Participant: __________________________

Signature: __________________________________

Date: ________________________________

_________________________________________  Date
Signature of Principal Investigator

or

_________________________________________  Date
Signature of Person Obtaining Consent

THIS FORM IS NOT VALID UNLESS THE FOLLOWING BOX HAS BEEN COMPLETED BY THE HIC OFFICE

VALID ONLY THROUGH:

______________________________
HR PROTOCOL #:  INITIALED:

______________________________

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Appendix C: Privacy Rule Authorization Form

YALE UNIVERSITY

Authorization To Use Personal Health Information In Research

Study Title: The Effect of Pregabalin in Patients With Phantom Limb Pain: A Randomized Controlled Trial

Principal Investigator(s): Brandon Beattie, PA-SII and Huned Patwa, MD

Participant Name: ____________________________________________________________

Medical Record Number: _____________________________________________________

Before researchers use or share any health information about you as part of this study, Yale University is required to obtain your authorization. This helps explain to you how this information will be used or shared with others involved in the study.

- Yale University and its hospitals, clinics, health-care providers and researchers are required to protect the privacy of your health information.

- You should have received a Notice of Privacy Practices when you received health care services here. If not, let us know and a copy will be given to you. Please carefully review this information. Ask if you have any questions or do not understand any parts of this notice.

- If you agree to take part in this study your health information will be used and shared with others involved in this study. Also, any new health information about you that comes from tests or other parts of this study will be shared with those involved in this study.

- Health information about you that will be used or shared with others involved in this study may include your research record and any health care records at Yale University. For example, this may include your medical records, x-ray or laboratory results. Psychotherapy notes in your health records (if any) will not, however, be shared or used. Use of these notes requires a separate, signed authorization.

Please read the information carefully before signing this form. Please ask if you have any questions about this authorization, the University’s Notice of Privacy Practices or the study before signing this form.

Initials/Date: _______________
Those Who May Use, Share and Receive Your Information As Part Of This Study

- Researchers and staff at Yale University will use, share and receive your personal health information for this research study. Authorized Yale staff not involved in the study may be aware that you are participating in a research study and have access to your information. If this study is related to your medical care, your study-related information may be placed in your permanent hospital, clinic or physician’s office records.

- Those who oversee the study will have access to your information, including:
  o Members and staff of Yale University’s Institutional Review Board (IRB) and Human Investigation Committee (HIC)
  o University data safety monitoring committees
  o Yale University Office of Research

- Your health information may also be shared with federal and state agencies that have oversight of the study or to whom access is required under the law. These may include:
  o The Food and Drug Administration
  o The National Institutes of Health

Authorization Period

- This authorization will not expire unless you change your mind and revoke it in writing. There is no set date at which your information will be destroyed or no longer used. This is because the information used and created during the study may be analyzed for many years, and it is not possible to know when this will be complete.

Signing the Authorization

- You have the right to refuse to sign this authorization. Your health care outside of the study, payment for your health care, and your health care benefits will not be affected if you choose not to sign this form.

- You will not be able to take part in this study and will not receive any study treatments if you do not sign this form.

- If you sign this authorization, you may change your mind at any time. Researchers may continue to use information collected up until the time that you formally changed your mind. If you change your mind, your authorization must be revoked in writing. To revoke your authorization, please write to:
  
  Brandon Beattie, PA-SII
  Yale School of Medicine
  333 Cedar Street
  New Haven, CT 06510

Initials/Date: _______________
• Signing this authorization also means that you will not be able to see or copy your study-related information until the study is completed. This includes any portion of your medical records that describes study treatment.

Contacts for Questions

• If you have any questions relating to your privacy rights, please contact Brandon Beattie, PA-SII or Huned Patwa, MD

Signature

I have read (or someone has read to me) this form and have been able to ask questions. All of my questions about this form have been answered to my satisfaction. By signing below, I permit Brandon Beattie, PA-SII and Huned Patwa, MD and the others listed on this form to use and share my personal health information for this study. I will be given a copy of this signed form.

Signature

( Participant or Legally Authorized Representative)

Name

(Print name above)

(If legal representative, also print relationship to participant.)

Date Time AM / PM

Initials/Date: ______________
Appendix D: NRS Pain Scale

A

Select the number that best describes your neuropathic pain during the past 24 hours. (Circle one number only)

0 1 2 3 4 5 6 7 8 9 10

No pain Worst possible pain

B

Since the start of the study, my overall status is:

1 □ Very Much Improved
2 □ Much Improved
3 □ Minimally Improved
4 □ No Change
5 □ Minimally Worse
6 □ Much Worse
7 □ Very Much Worse

Appendix E: LANSS

The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) Pain Scale

Name ................................................................. Date ........................................

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find this out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly.

1. Does your pain feel like strange, unpleasant sensations in your skin?
   Words like pricking, tingling, pins and needles might describe these sensations.
   a) NO – My pain doesn’t really feel like this .......................................................... (0)
   b) YES – I get these sensations quite a lot .......................................................... (5)

2. Does your pain make the skin in the painful area look different from normal?
   Words like mottled or looking more red or pink might describe the appearance.
   a) NO – My pain doesn’t affect the colour of my skin ........................................... (0)
   b) YES – I’ve noticed that the pain does make my skin look different from normal .... (5)

3. Does your pain make the affected skin abnormally sensitive to touch?
   Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.
   a) NO – My pain doesn’t make my skin abnormally sensitive in that area ............... (0)
   b) YES – My skin seems abnormally sensitive to touch in that area ....................... (3)

4. Does your pain come on suddenly and in bursts for no apparent reason when you’re still?
   Words like electric shocks, jumping and bursting describe these sensations.
   a) NO – My pain doesn’t really feel like this .......................................................... (0)
   b) YES – I get these sensations quite a lot .......................................................... (2)

5. Does your pain feel as if the skin temperature in the painful area has changed abnormally?
   Words like hot and burning describe these sensations.
   a) NO – I don’t really get these sensations ....................................................... (0)
   b) YES – I get these sensations quite a lot ....................................................... (1)
Leeds Assessment of Neuropathic Symptoms and Signs (continued)

B. SENSORY TESTING

Skin sensitivity can be examined by comparing the painful area with a contralateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1. Allodynia

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO – Normal sensations in both areas ....................................................................................................................... (3)
b) YES – Alodynia in painful area only .......................................................................................................................... (5)

2. Altered pin-prick threshold

Determine the pin-prick threshold by comparing the response to a 23-gauge (blue) needle mounted inside a 2ml syringe barrel placed gently onto the skin in a non-painful and then painful areas.

If a sharp pin prick is felt in the non-painful area, but a different sensation is experienced in the painful area, eg. none/ blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO – Equal sensation in both areas .......................................................................................................................... (3)
b) YES – Altered PPT in painful area .......................................................................................................................... (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) ............................................................................................................................................... 

If score < 12, neuropathic mechanisms are unlikely to be contributing to the patient’s pain.
If score ≥ 12, neuropathic mechanisms are likely to be contributing to the patient’s pain.

Appendix F: SF-36 Health Survey Form

SF-36 QUESTIONNAIRE

Name:______________________  Ref. Dr:______________________  Date:_______

ID#:______________________  Age:_______  Gender: M / F

Please answer the 36 questions of the Health Survey completely, honestly, and without interruptions.

GENERAL HEALTH:
In general, would you say your health is:
☐ Excellent  ☐ Very Good  ☐ Good  ☐ Fair  ☐ Poor

Compared to one year ago, how would you rate your health in general now?
☐ Much better now than one year ago
☐ Somewhat better now than one year ago
☐ About the same
☐ Somewhat worse now than one year ago
☐ Much worse than one year ago

LIMITATIONS OF ACTIVITIES:
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports.
☐ Yes, Limited a lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Lifting or carrying groceries
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Climbing several flights of stairs
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Climbing one flight of stairs
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Bending, kneeling, or stooping
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Walking more than a mile
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Walking several blocks
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all

Walking one block
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all
Bathing or dressing yourself  
☐ Yes, Limited a Lot  ☐ Yes, Limited a Little  ☐ No, Not Limited at all  

PHYSICAL HEALTH PROBLEMS: 
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? 

Cut down the amount of time you spent on work or other activities  
☐ Yes  ☐ No  

Accomplished less than you would like  
☐ Yes  ☐ No  

Were limited in the kind of work or other activities 
☐ Yes  ☐ No  

Had difficulty performing the work or other activities (for example, it took extra effort)  
☐ Yes  ☐ No  

EMOTIONAL HEALTH PROBLEMS: 
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)? 

Cut down the amount of time you spent on work or other activities  
☐ Yes  ☐ No  

Accomplished less than you would like  
☐ Yes  ☐ No  

 Didn't do work or other activities as carefully as usual  
☐ Yes  ☐ No  

SOCIAL ACTIVITIES: 
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?  
☐ Not at all  ☐ Slightly  ☐ Moderately  ☐ Severe  ☐ Very Severe  

PAIN: 
How much bodily pain have you had during the past 4 weeks?  
☐ None  ☐ Very Mild  ☐ Mild  ☐ Moderate  ☐ Severe  ☐ Very Severe  

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?  
☐ Not at all  ☐ A little bit  ☐ Moderately  ☐ Quite a bit  ☐ Extremely
Bathing or dressing yourself
- Yes, Limited a Lot
- Yes, Limited a Little
- No, Not Limited at all

PHYSICAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?
- Cut down the amount of time you spent on work or other activities
  - Yes
  - No
- Accomplished less than you would like
  - Yes
  - No
- Were limited in the kind of work or other activities
  - Yes
  - No
- Had difficulty performing the work or other activities (for example, it took extra effort)
  - Yes
  - No

EMOTIONAL HEALTH PROBLEMS:
During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?
- Cut down the amount of time you spent on work or other activities
  - Yes
  - No
- Accomplished less than you would like
  - Yes
  - No
- Didn't do work or other activities as carefully as usual
  - Yes
  - No

SOCIAL ACTIVITIES:
Emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?
- Not at all
- Slightly
- Moderately
- Severe
- Very Severe

PAIN:
How much bodily pain have you had during the past 4 weeks?
- None
- Very Mild
- Mild
- Moderate
- Severe
- Very Severe

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely
ENERGY AND EMOTIONS:
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.

Did you feel full of pep?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you been a very nervous person?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you felt so down in the dumps that nothing could cheer you up?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Have you felt calm and peaceful?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time

Did you have a lot of energy?
☐ All of the time
☐ Most of the time
☐ A good Bit of the Time
☐ Some of the time
☐ A little bit of the time
☐ None of the Time
Have you felt downhearted and blue?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel worn out?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Have you been a happy person?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

Did you feel tired?
- All of the time
- Most of the time
- A good Bit of the Time
- Some of the time
- A little bit of the time
- None of the Time

SOCIAL ACTIVITIES:
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?
- All of the time
- Most of the time
- Some of the time
- A little bit of the time
- None of the Time
GENERAL HEALTH:
How true or false is each of the following statements for you?

I seem to get sick a little easier than other people
- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false

I am as healthy as anybody I know
- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false

I expect my health to get worse
- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false

My health is excellent
- Definitely true
- Mostly true
- Don't know
- Mostly false
- Definitely false

## Appendix G: Pain Diary

For each time slot, write down what you were doing and how much pain you were in.

<table>
<thead>
<tr>
<th>Time Slot</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
<th>Saturday</th>
<th>Sunday</th>
</tr>
</thead>
<tbody>
<tr>
<td>7am to 9am</td>
<td></td>
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<tr>
<td>9am to 10am</td>
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<tr>
<td>10am to 11am</td>
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<tr>
<td>11am to 12pm</td>
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<td>7 to 8</td>
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<td>8 to 9</td>
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<td>9 to 10</td>
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<tr>
<td>10 to 12pm</td>
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</tbody>
</table>
Appendix H: Sample Size Calculation

In order to estimate the sample size, a T test calculator (Power and Precision version 4. 2000 Biostat, Inc. Engelwood, NJ.) was used to compare two independent means for a two-sided alpha of 0.05 and a power of 80%. To detect a mean change in patient-reported pain of 1.3 from baseline using the NRS Pain Scale using a standard deviation of 2.5, 71 participants will be required in each arm of the study for a total sample size of 142 participants. The effect size was assumed using similar studies that have demonstrated a mean change in patient-reported pain of 1.3 from baseline as being statistically significant. The dropout rate for this study was estimated to be 20% to take into account the higher than usual attrition rates demonstrated in previous pain studies when compared to other randomized controlled trials.

<p>| | |</p>
<table>
<thead>
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<th></th>
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<tr>
<td><strong>Alpha</strong></td>
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<tr>
<td><strong>Power</strong></td>
<td>0.80</td>
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<tr>
<td><strong>Beta</strong></td>
<td>0.20</td>
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<tr>
<td><strong>Standard Deviation</strong></td>
<td>2.5</td>
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<tr>
<td><strong>Mean Change In Patient-Reported Pain From Baseline Using NRS Pain Scale</strong></td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Estimated Attrition Rate</strong></td>
<td>20%</td>
</tr>
<tr>
<td><strong>Calculated Sample Size (Per Arm)</strong></td>
<td>71 participants in each arm of the study</td>
</tr>
<tr>
<td><strong>Total Study Sample Size</strong></td>
<td>142 participants</td>
</tr>
</tbody>
</table>
Bibliography


46. van Severen R, Feister HA, Young JP, Jr., Stoker M, Versavel M, Rigaudy L. Efficacy and tolerability of twice-daily pregabalin for treating pain and related...


