ABSTRACT

A COMPARISON OF PAIN NEUROPHYSIOLOGY EDUCATION WITH THERAPEUTIC INTERVENTIONS VERSUS THERAPEUTIC INTERVENTIONS ALONE ON PAIN AND FUNCTION IN INDIVIDUALS WITH CHRONIC LOW BACK PAIN: A META-ANALYSIS

Objectives: The purpose of this meta-analysis is to assess the effectiveness of pain neurophysiology education with therapeutic interventions versus therapeutic interventions alone on pain and function in individuals with chronic low back pain.

Methods: Studies analyzing therapeutic interventions with pain neurophysiology education compared to therapeutic interventions alone were examined. Data from these studies with similar subgrouping were analyzed to determine treatment effect size and homogeneity.

Results: Four studies were included in this meta-analysis. The combination of pain neurophysiology education and therapeutic intervention demonstrated a larger treatment effect for both pain and function. However, statistical significance was established for pain only. Heterogeneity was found in both groups.

Conclusion: Findings within this meta-analysis reveal that pain neurophysiology education combined in adjunct to therapeutic interventions has a greater treatment effect size when compared to therapeutic interventions alone.

Study Design: A meta-analysis of randomized controlled trials examining the effects of a pain neurophysiology education with therapeutic interventions compared to therapeutic interventions alone.

Justin Yun
May 2017

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BACKGROUND

Introduction

The global prevalence of low back pain (LBP) has steadily increased over the past few decades. It is currently the leading cause of disability worldwide and is associated with significant economic burden. In the United States, direct healthcare and indirect (loss of work productivity) cost on the economy are approximately $84.1 billion.[1,2] An estimated 80% of the general population experiences an episode of LBP in a lifetime.[3,4] Several individual and activity based factors associated with developing LBP include gender, with woman having an increased incidence, increasing age, lifestyles (i.e. smoking, obesity), and occupation.[5] There are, however, variations in regards to the prevalence and characteristics of chronic low back pain (CLBP). Roughly 23% of the individuals with LBP develop CLBP, presenting with significant functional limitations, intense pain, and activity limitations.[2,6] Studies show individuals with CLBP are more likely to seek healthcare services, ultimately contributing to the majority of direct and indirect costs.[3]

Imaging is commonly used in the examination process, the primary method in determining an anatomical relationship for LBP. However, studies demonstrate that abnormal radiographic images do not always provide an accurate estimation of the relationship to back pain. Savage et al.[7] found 32% of individuals with radiologic findings of degeneration or herniation in the lumbar spine were not symptomatic, and 47% of individuals who had normal findings had symptomatic complaints. Delitto et al.[8] compared surgical intervention to physical therapy for individuals identified by imaging for symptomatic lumbar stenosis. After a 2-year follow-up, the findings revealed both surgery and physical therapy had similar

outcomes in pain and function. Therefore, in some individuals, the surgical site was not the primary source of pain, as symptoms did not completely resolve. These findings propose a host of possibilities; 1) that the source of pain is not solely from injury to anatomical structures, 2) that alternative processes contribute to pain symptoms and CLBP is a multifactorial problem.

Understanding the complexities of managing individuals with CLBP requires a discussion of healthcare frameworks and an updated scientific foundation to implement interventions. The biomedical model is a traditional approach to treating disease.[9] This model focuses on the causal relationship between biological dysfunction and pain or disability, implying treatment of the biological dysfunction will alleviate symptoms and allow for recovery. This approach works well with a pathology such as disc protrusion, but falls short when explaining the persistence of pain when the biological dysfunction is absent or not clearly identified. In 1977, Engel introduced the biopsychosocial model where he suggested cultural, social, and psychological components, in addition to biological factors, should be considered to properly address a disease.[10] Gordon Waddell, an orthopedic surgeon, also recognized the importance of this approach and popularized the utilization of the concept in treating individuals with CLBP.[11]

Management of CLBP encompasses a range of different treatment strategies including pharmacotherapy, invasive treatments, and conservative treatments.[3] Medications such as Non-steroidal anti-inflammatory drugs (NSAIDs), muscle relaxants, and opioids have a moderate effect in decreasing pain in the short term. However, the effects of opioids are variable and includes risks of dependency.[12] Surgical procedures also present variable outcomes, with failure rates estimated to be between 10-40%.[13] Conservative treatments which include modalities, exercise therapy, aquatic therapy, manual therapy, and

education generally demonstrated a modest treatment effect.[14,15] Airaksinen et al.[16] reported there is no superior intervention in the treatment of individuals with CLBP who present with disability and long duration. Waddell reiterates this claim, stating that the therapeutic options become limited, as interventions do not effectively address the mechanisms of chronic pain.[17] Thus, the development of an intervention model that addressed the complexities of chronic pain was created.

In terms of a deeper comprehension of pain, in 1965, Melzack and Wall[18] provided the first scientific breakthrough. The Gate Control Theory of pain proposed the central nervous system (CNS) was an essential component in pain perception. The dorsal horn of the spinal cord acts as a gate keeper, which inhibits or allows pain transmission from the periphery to the brain. Additional factors are the diameter of peripheral sensory fibers, as well as descending information from the brain. The theory established a foundation for researchers to integrate psychological and cognitive components such as experience, stress, or memory as contributors in the pain process. However, studies yielded questions that eventually required a new framework to explain conditions that did not fit the model such as phantom or chronic pain. This led Melzack to develop a conceptual model termed neuromatrix.[19-21] The neuromatrix model is a dynamic network of neurons creating neuronal maps through various cortical structures, creating patterns, or neurosignatures, leading to a multidimensional experience of pain. Lorimer Moseley, a clinical researcher well known in the field of pain neuroscience, incorporated principles from the pain neuromatrix model to develop a clinical approach to treat chronic pain.[22]

In 2002, Moseley conducted a study determining the efficacy of a program (Explain Pain) that educated individuals with CLBP on the neurophysiology of pain rather than the traditional educational model, which have focused on anatomy

and physiology of the lumbar spine.[23,24] He found traditional physical therapy combined with Explain Pain was more effective in decreasing pain and improving function than when physical therapy interventions were administered in isolation. Chronic low back pain is a multidimensional entity with structural, social and psychological factors. Therefore, a model incorporating these factors creates a more efficacious and balanced program with improved outcomes would provide additional support for research in the developing field of pain neurophysiology education. Furthermore, while improving the quality of life in individuals there are additional benefits such as decreasing direct and indirect healthcare costs. Therefore, the purpose of this meta-analysis is to compare traditional physical therapy versus physical therapy with pain neurophysiology education to determine which program will provide better outcomes in pain and function.

Background

Low Back Pain

Approximately 25% of U.S. adults experience LBP in at least once within the last 3 months.[12] Low back pain (LBP) is considered acute when symptoms resolve within 1 month, subacute between 2-3 months, and chronic when it lasts longer than 3 months. Studies have found the highest prevalence occurs among women and individuals aged between 40 and 80 years.[25] Prevalence of occupational LBP varies by region and occupation, statistics range from 9-26% of workers' compensation claims. Approximately 8% of the U.S. work force is absent from work for an average of 9 workdays per year.[26] The increasing incidence of LBP in the U.S. has led to a 65% increase in healthcare expenses related to LBP.[27]

Anatomically, the spine is a complex system that protects and houses the spinal cord, nerve roots, and the vascular supply. There are 5 divisions of the spine: cervical, thoracic, lumbar, sacral, and coccygeal. Each region presents with unique qualities that help stabilize the head and trunk while the limbs are moving. Structural components of the spine include: vertebrae, neural arch, intervertebral discs, zygapophyseal joints, ligaments, fascia, and muscles. The mechanoreceptors within bones, disks, and ligaments transmit information from the spinal structures to the central nervous system (CNS) which coordinates the appropriate muscles, movement patterns, and reflexes. Damage to any of the spinal components compromises the spine's foundation, leading to instability, accelerated degeneration, and pain.[28]

Low back pain is defined as pain and discomfort bordered by costal margins and gluteal folds, with or without referred leg pain. Individuals with LBP are classified into specific or nonspecific LBP.[1] Specific LBP identifies a pathology such as hernia nucleus pulposus, ankylosing spondylitis, osteoporosis, etc. and accounts for 10% of all LBP.[29] In 90% of individuals with chronic LBP, there is no evident structural damage or clear pathology. Low back pain affects most individuals at some point in their lives, frequently resulting in significant physical impairments such as pain, muscle imbalances, and disability. However, LBP is a complex disorder, which can be influenced by various factors. These include cognitive (i.e. catastrophizing beliefs, poor motivation), psychological (i.e. anxiety, depression, emotional), or social (i.e. cultural, responsibilities with work or family) factors. These factors contribute to prolonged disability and poor prognosis in some individuals who transition from acute to chronic stages of LBP.

Therefore, pain is a multifactorial entity, and is defined by the International Association of Study of Pain (IASP)[30] as an unpleasant sensory and emotional

experience associated with actual or potential tissue damage, or described in terms of such damage. The primary purpose of pain is to protect the body by producing a predictable physiologic response (increased muscle tone, heart rate, respiratory rate, etc.) to injury, driving the individual to prioritize and address the pain accordingly. A major feature of pain is neuronal plasticity, where changes (short-term or long-term) in neurotransmitters, receptors, interneurons, and the cerebral cortex occur as a response to tissue or structural injury, inflammation, or disease. This process can induce negative or positive neuronal plasticity, thus influences the experience of pain.[31]

Pain physiology is a complex interaction of cellular inflammation, pain transmission, and pain perception. The experience of pain begins with inflammation and subsequent cellular responses. Injury can occur from physical traumas such as a sprain, contusion, or fracture. In addition, it can also occur from chemical, bacterial or viral infections, or heat. The inflammatory response begins and progresses in 3 predictable stages: 1. Inflammatory response, 2. Repair and regeneration, and 3. Remodeling and maturation.[32] An acute injury triggers the release of local cytokines and other inflammatory mediators, creating changes in local blood flow and migration of specialized cells to initiate the healing process. This causes a cellular cascade of changes: 1. immune cells (Histamine, Prostaglandins, nitric oxide, tumor necrosis factor alpha, interleukin 1-alpha, interleukin 1-beta, interleukin-4, interleukin-6, and interleukin-8, serotonin); 2. Nerve cells (Substance P, glutamate, neurokinin A, and vasoactive intestinal peptide) and; 3. Vessels (calcitonin gene related peptide). These cellular changes lead to physical signs and symptoms of pain, warmth, swelling, and tenderness to palpation.[33]

Sensory free nerve endings or nociceptors located in the lumbar spine include spinal muscles, spinal ligaments, facet joint, disc, vertebrae, and dura. Cytokines and other inflammatory mediators initiate pain transmission by altering the balance of sodium and calcium ions across the synaptic junction, leading to action potentials that propagate nociceptive input via A-delta (myelinated) and C-fibers (non-myelinated) into cell bodies located within the dorsal horn of the spinal cord, specifically the substantia gelatinosa (SG).

In the dorsal horn, first-order sensory neurons are modulated and transmitted to second-order neurons by neurotransmitters in the SG.[34] These second order neurons display different firing thresholds, resulting in either reflexive movements, autonomic activation, or higher center processing. Nocioceptive information decussates at entry level and ascends via anterolateral tract towards the thalamus, where information is relayed to several higher centers. The anterolateral tract is 1 of 2 major pathways that primarily transmits sensory information which includes crude touch, pressure, temperature, and pain. The second major ascending pathway is dorsal column medial lemniscal that transmits innocuous sensory information (vibration, discriminative touch, and proprioception) towards the brain. Each tract sends information that contributes to an individual's ability to perceive, interpret, and develop memories of pain.

In addition to ascending pathways, the central nervous system (CNS) consists of pain pathways that either inhibit or facilitate the perception of pain at the dorsal horn. These structures include the prefrontal cortex, anterior cingulate, amygdala, hypothalamus, periaqueductal gray (PAG), and rostral ventromedial medulla (RVM).[35,36] Pain modulation is primarily mediated by descending monoaminergic pathways that utilize neurotransmitters serotonin, norepinephrine, or dopamine.[37] The PAG and RVM are believed to be responsible for the

descending endogenous pain pathway. These regions are responsible for stressed induced analgesia, which have been observed in highly stressful situations such as injuries during war.

The PAG receives input from the cortex (frontal and insular cortex, amygdala, and hypothalamus) and descends to the RVM and brainstem.[36] The stress induced analgesia is mediated by the descending pathway from the amygdala, PAG, and RVM. Neurotransmitters from the RVM travel down to the dorsal horn via raphespinal tracts and releases serotonin which inhibits the transmission of pain by binding to the enkephalin interneuron of the C-fiber receptors and A-delta fibers.[37] The activation of the opioid receptors inhibits the release of substance P and furthermore, prevents transmission of pain impulses through the spinothalamic tract. Overall, the stimulation of the PAG produces analgesia. The descending pathway activates in acute pain to protect the individual from further environmental injury. However, persistent transmission of nociceptive input can disrupt the balance of inhibitory and facilitatory relationship in both ascending and descending pain modulating systems in individuals with CLBP, which can alter the experience of pain.[38]

Though pain usually results from injury or tissue damage, neuropathic pain originates from a lesion or disease affecting the nervous system.[39] Neuropathic pain is a frequent problem in peripheral (diabetes, nerve trauma, carpal tunnel) and central nervous system (stroke, multiple sclerosis, spinal cord injury) diseases, often resulting in chronic pain. Symptoms associated with neuropathic pain include widespread pain, sensory deficits, burning pain, allodynia, with variable bursts without provocation. These symptoms vary among individuals and can occur simultaneously with injury or tissue damage.

Peripheral and Central Sensitization

Both nociceptive and neuropathic pain exhibit neuroplastic features through a process known as sensitization. Under normal circumstances, nociceptors exhibit high threshold to stimulation, where they are considered "sleeping" or inactive. When tissues are damaged, inflammatory mediators activate the sleeping nociceptors and become extremely reactive to stimuli; this is known as peripheral sensitization.[35] The primary mechanism responsible for modifying pain transmission is the phosphorylation of receptor and ion channels, which alters the cell properties of the peripheral nociceptors and neurons in the dorsal horn. Exposure to inflammatory mediators initiates cellular changes to peripheral nociceptors, leading to the desensitization of sensory resistant neurons by altering sodium ion channels. The process lowers the threshold for nociceptors to depolarize, resulting in increased sensitivity to stimuli or hyperalgesia.[40]This is common post ankle sprains where an individual would continue to experience pain, even with partial weight bearing. An individual who presents with acute lumbar facet impingement would have pain with the slightest movement. Peripheral sensitization is a result of an evolutionary response to protect the injured tissue from further damage.

Persistent transmission of pain signals from nociceptors to the dorsal horn can create neuroplastic changes in the central nervous system (CNS), triggering central sensitization (CS). Central sensitization is an increased responsiveness in the CNS to nociceptors or innocuous sensory input, resulting in hypersensitivity.[30] Central sensitization begins with a cascade of intracellular events in the dorsal horn of the spinal cord. The acute phase of CS is activity-dependent synaptic plasticity, where nociceptor input triggers the release of neurotransmitters such as substance P and glutamate in the dorsal horn, activating N-methyl-D-aspartate

(NMDA) receptors.[41] The upregulation of NMDA increases the excitability to glutamate, prolonging the transmission of pain. When pain continues to persist after the tissue has healed, the late-onset phase of CS begins to occur. Proteins such as prostaglandins are produced which continues to increase excitability, consequently, in addition to prolonged pain, individuals with CLBP begin to report of secondary hyperalgesia or diffuse pain across the lower back. Sensitization can continue to occur and lead to potentially permanent changes as neuroimmune and structural reorganization begins to develop in the dorsal horn.[41]

The inhibitory interneurons act as pain modulators in the dorsal horn. Larger myelinated ascending sensory fibers or descending inputs release inhibitory transmitters, which act on the inhibitory interneurons, limiting the transmission of pain. However, persistent activity from peripheral nociceptors, particularly C-fibers, leads to excessive saturation of glutamate in the dorsal horn, resulting in cell death.[40-42] Structural changes have been observed in individuals with allodynia, where alpha-beta fibers sprout towards the superficial layers of the lamina and override nociceptor terminals when synapsing with second order neurons.[41] These abnormal central changes from CS (hyperalgesia, secondary hyperalgesia, and allodynia) may be present in individuals with CLBP, contributing to the difficulty for healthcare practitioners to provide effective treatment.[43]

Chronic Pain

As individuals go through their daily life, there is a healthy balance of inhibitory and facilitatory regulation of sensory information within the nervous system. However, when an individual is suffering from persistent pain such as CLBP, negative neuroplastic changes occur throughout the CNS.[41] Central

sensitization is an important feature in many individuals with chronic pain syndromes including, but not limited to, those with whiplash, osteoarthritis, fibromyalgia, and CLBP. Chronic pain (CP) is defined as pain persisting for more than 6 months after the noxious stimulus or damaged tissue has resolved.[30] Individuals with CP present with hypersensitive nociceptors, enlarged receptive fields, secondary hyperalgesia and allodynia, and alterations to the descending endogenous pain modulatory pathways. These changes to the nervous systems as mentioned earlier, are a result of central sensitization. Nociceptive input towards the higher centers are mediated by chemically excitatory transmitters, glutamate and tachykinins.[44] In CP, tachykinins are thought to be involved in prolonged glutamate activity, which enhances pain. Imaging in individuals with CP have found decreased density of brain gray matter and altered descending pain modulating systems.[45] Because of the widespread findings in individuals with CP, prescribing an appropriate intervention plan that targets multiple areas remains a challenging issue for healthcare practitioners. Chronic low back pain is no longer limited to a pathoanatomical cause. Due to the complexity of the pain experience, guidelines for LBP treatment have generally shifted towards a biopsychosocial management approach, in which treatment addresses the biological, psychological and social ramifications of chronic pain.[46]

Management of CLBP

Generally, physical therapy interventions target muscles and joints or improving motor control as means of improving CLBP. The current Clinical practice guidelines[5] recommend Grade A interventions such as manual therapy, trunk coordination, strengthening, endurance training, centralization or directional preference, and fitness activities when treating individuals with CLBP. However,

Fritz et al.[47] states that despite the numerous randomized control trials examining the effectiveness of conservative management and surgical interventions, the evidence remains inconclusive and contradictory. Airaksinen et al.[16] further supports that a single intervention is not likely to be an effective treatment for CLBP, particularly in individuals presenting with longer duration and increased disability.

Though conservative interventions such as motor control and spinal manipulation have been shown to relieve pain and function, over time, the effects are similar to general exercise.[14] An intensive aquatic therapy has demonstrated long term improvements in function and quality of life, but it requires individuals to exercise 5 times per week, 60 minutes each session to achieve similar long term outcomes.[48] This is not a feasible option for most individuals with CLBP. In addition to CP, individuals must contend with negative psychological processing, namely depression and anxiety. Psychosocial factors such as an individual's attitude and coping mechanism are critical factors in the development and maintenance of CLBP, and thus play a significant role in the prognosis. Therefore, behavioral approaches such as cognitive behavioral therapy in addition to a multimodal approach, which includes conservative management (modalities, exercise, education) and pharmacotherapy, have increasingly been utilized to treat CLBP.[12,49]

Pain Education

The goal of a biopsychosocial approach is to change the individual's attitude and expectations about their ability to control pain. Traditional patient education informs individuals of possible anatomical components (injured tissue), biomechanics (abnormal movement patterns), and pathoanatomy (degeneration) as

the source of pain.[50] Although informative, this educational approach does not explain the complexities of chronic pain such as peripheral mechanisms, pain centralization or neuroplasticity. Traditional patient education has been found to have limited effectiveness in decreasing pain and disability.[51] Additionally, an opposite effect has been found with some individuals showing increases in stress and anxiety.[52] Patients previously educated on the pathology of disc herniation still accept that the source of their pain is the main pathology several years later. Due to the increasing incidence of CLBP and limited efficacy of interventions, such as patient education in relieving pain and improving function, a new educational intervention was developed in the early 2000s to help clinicians and individuals address chronic pain.[53]

David Butler and Lorimer Moseley developed Explain pain (EP),[53] an educational intervention which aims to help healthcare practitioners teach individuals about the neurophysiology of pain. The primary objective of EP is to teach individuals to re-conceptualize the meaning of pain. Due to the multidimensional nature of pain, EP utilizes the biopsychosocial model to promote self-efficacy within individuals. Changing an individual's perception of pain can help develop confidence and encourage movement, exercise, and daily activities.[54] In 2011, a systematic review of 8 randomized control trials concluded that educating individuals with chronic pain about the neurophysiology of pain had positive effects on pain perception, disability, and catastrophization.[55]

Pain neurophysiology education has demonstrated effectiveness when used in isolation for the treatment of CLBP.[56] However, there is little evidence about the impact on pain and function when utilizing PNE in adjunct to physical therapy interventions. A recent study compared aquatic exercise and pain neurophysiology education (PNE) to aquatic exercise alone in individuals with chronic low back

pain (CLBP).[57] The results of the study found the education group with aquatic therapy was consistently favored in decreasing pain after the 6-week post-intervention and the 12-week follow-up. There is emerging evidence to support PNE in combination with therapeutic interventions.[56-58] However, the overall clinical significance of therapeutic interventions with PNE in individuals with CLBP has not yet been fully established.

The cost-effectiveness of an intervention with a significant low risk-benefit ratio in favor of PNE would be appealing to insurance providers and physical therapists.[54] Additionally, due to the socioeconomic burden and increasing prevalence of CLBP, studies demonstrating statistical and clinical significance for PNE in improving pain and function would benefit everyone involved in the care for the individual with CLBP. This study will fill a gap in the literature by providing supportive research for the effectiveness of a pain education model for the management of pain in order to improve the delivery of care for individuals with CLBP. Therefore, the null hypothesis states that there will be no significant difference in the pain scales and functional disability questionnaires with the combination of PNE and therapeutic interventions, compared to therapeutic interventions alone in individuals with chronic low back pain. The alternative hypothesis states there will be statistically significant difference between therapeutic interventions with PNE and therapeutic interventions alone.

METHODS

Search Strategy

One reviewer performed a study eligibility assessment in a standardized manner. The meta-analysis was structured by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 27-item checklist. An electronic search included the following databases: PubMed, CINAHL, PEDro, Cochrane library, and Google Scholar with the following search terms: pain education, pain science, chronic low back pain, pain neuro* education, therapeutic neuroscience education, explain pain, and Moseley and Butler. The search began in August 2016 and concluded November 2016. After obtaining the articles, an inclusion and exclusion criteria was utilized to filter articles appropriate for the meta-analysis. Additionally, a manual search was performed to identify relevant articles through reference lists from other sources. The articles were limited to peer-reviewed journals from the years 1995-2016 written in English.

Inclusion and Exclusion Criteria

Studies included in this meta-analysis were based on the following criteria: a randomized controlled trial (RCT), males and females between the ages of 18-65 with chronic low back pain for > 3 months, incorporating the explain pain manual developed by Butler and Mosely in 2003, and providing outcome measures that assess the intensity of pain and functional disability. Studies were excluded on the following criteria: a diagnosis of low back pain due to underlying pathology (tumor, infection, or inflammatory disorder), history of low back surgery, diagnosis of fibromyalgia, history of conservative management within the last 3 months, and low back pain with nerve root irritation or fractures.

Quality Assessment

The articles selected for this meta-analysis were scored using the 11-point PEDro scale[59], however the final score excludes the first criterion. This scale assisted the reviewer in examining various areas of validity and risk for bias of each study. The range for the PEDro scores are as follows: 6-10, 4-5, and 1-3 which are represented as high quality, fair quality, and poor quality respectively. See Table 1 for complete quality assessment of studies included.

Outcome Measures Studied

Low back pain intensity was recorded using either the Visual Analog Scale (VAS)[60] or the Numeric Rating Scale (NRS) [61,62]. The VAS and NRS are subjective measures of pain which have been proven to be a reliable and valid tool in measuring pain intensity.[60-62] They also highly correlate with each other. The VAS is comprised of a horizontal or vertical line between 0-10 cm where 0 represents no pain and 10 represents the worst imaginable pain. There are various forms of NRS utilized throughout literature, the 0-100 scale was assessed with the studies included in this review. Zero represents no pain at all whereas 100 represents the worst pain ever possible. Function was measured by the Roland Morris Disability Questionnaire (RMDQ)[63] and Quebec Back Pain Disability Scale (QBPDS).[64] The RMDQ is a 24-item questionnaire about how LBP affects functional activities. Each question is worth 1 point and ranges from 0 (no disability) to 24 (severe disability). The QBPDS is a questionnaire developed to measure the level of functional disability for individuals with LBP. The QBPDS consists of 20 daily activities that can be subcategorized into 6 activities. The RMDQ and QBPDS demonstrates good reliability and validity, as well as high correlation with each other.[63,64]

Statistical Analysis

The OpenMetaAnalyst[65] was utilized to determine the effect size and confidence intervals based on the mean and standard deviations presented in each study. The effect size determines the magnitude of the treatment effect and is categorized as small, medium, and large with the cut-off values of <0.30, 0.30-0.60, >0.60. CI with a 95% confidence interval provides statistical significance for individual studies and grand effect size. Forest plots were used to visualize the effect size of individual studies, comparison of studies and the grand effect size of the treatment effect in regards to pain and function. Homogeneity was tested by the Q statistic or I squared for the meta-analysis. Random, fixed effect size was computed on the effect size based upon homogeneity. In regards to pain and function, a decrease in score represents a decrease in pain and improved function, therefore a negative effect size favors a positive treatment effect.

RESULTS

Study Selection

An electronic search of several databases (PubMed, CINAHL, PEDro, and Cochrane library), produced 261 articles based on the following combination of keywords: pain neurophysiology education, therapeutic neuroscience pain education, and chronic low back pain. After a preliminary screen of duplicates, 227 remained. A review of titles and abstracts eliminated 207 articles because they did not meet the inclusion and exclusion criteria for chronic low back pain and pain education. Twenty full-text articles remained for in-depth review. Twelve of the articles were eliminated as they did not have the appropriate outcome measures, were not randomized controlled trials, and did not meet the inclusion criteria of utilizing the explain pain manual for pain education developed by Butler and Moseley.[53] Following the in-depth review, 4 studies remained that met the inclusion and exclusion criteria for this meta-analysis. Figure 1 provides a diagram of the study selection process.

The PEDro scale was developed to assess the quality of the randomized clinical trials (RCTs) to determine if the information provided from the studies could provide adequate statistical information to interpret the results. The PEDro score for all 4 studies was 8 out of a 10-point scale and level I evidence. The criteria not satisfied across all studies were blind therapists and blind assessors. Results of the PEDro scores are shown in Table 1.

Description of Studies

Four studies included in this meta-analysis met the inclusion and exclusion criteria based on population, intervention, outcome measures, and available statistical data. Two studies, Pires et al.[57] and Tellez-Garcia et al.[58] provided direct

comparisons of pain neurophysiology education (PNE) with an intervention, aquatic exercise and trigger point dry needling respectively, compared to the intervention alone. Ryan et al.[56] investigated the effects of PNE with general exercise, but unlike the previous studies, he compared the effects to PNE alone rather than the general exercise alone. Therefore, Ferreria et al.[14] was included in the meta-analysis to serve as a comparison, as it modeled the exercise class with the same authors.

Pires et al.[57] compared the effects of a 6-week aquatic exercise program with pain neurophysiology education (PNE) versus aquatic exercise alone. All participants engaged in a 30-50 min aquatic therapy program described by Dundar et al.[66] Pain neurophysiology education was provided prior to beginning the exercise program in 2 group sessions, 90-minutes each. Education addressed origin of acute pain, transition from acute to chronic pain, central sensitization, role of the brain in the perception of pain, psychosocial factors related to pain, flare-up management, and pacing. Metaphors and pictures were used to facilitate understanding of pain mechanisms. At 6 weeks, no statistically significant differences were found between the education and control group with both pain and function. However, at the 3 month follow up, the education group demonstrated statistically significantly greater reduction in pain and function. This study consistently favors the addition of PNE to the aquatic exercise program. Although both groups demonstrated improvement at the end of treatment, the PNE group continued to improve 3 months after treatment.

Tellez-Garcia et al.[58] examined the effects of trigger point dry needling (TrP-DN) with pain neurophysiology education (PNE) or TrP-DN alone. The study showed both treatments were effective for improving pain and disability, with no statistically significant differences between groups at the end of the 3-

week treatment program. Due to the similar reduction of pain intensity and disability, the results suggest TrP-DN was mainly responsible for these changes. However, the addition of PNE demonstrated statistically significantly greater reduction of kinesiophobia compared to TrP-DN alone, but the outcome measure assessing kinesiophobia was not included in this meta-analysis.

Ryan et al.[56] and Ferreira et al.[58] were evaluated together to determine the effects of general exercise alone or combined with pain neurophysiology education (PNE). Ryan et al. provided PNE in a 1, 2 and half-hour session that focused on reshaping the participant's beliefs and attitudes about their back pain. These individuals attended 6 exercises classes, once a week for 6 weeks. The classes were modeled after the 'Back to Fitness' program described by Moffett and Frost,[67] which involved a circuit based, graded, aerobic exercise with core stability exercises. Ferreira et al. also provided an exercise class based on the 'Back to Fitness' program, but included 12 treatments for 8 weeks. Both studies examined pain (NRS and VAS) and function outcome measures (RMDQ). After 6 weeks of treatment and 1 PNE session, Ryan et al. found clinically significant reduction in pain but statistically insignificant changes with the RMDQ. However, Ferreira et al. found a statistically significant difference with RMDQ at 8 weeks, but insignificant difference with pain. These studies suggest the addition of PNE is effective in decreasing pain, but does not improve function.

All 4 studies assessed in this meta-analysis were level I with an 8 out of 10 PEDro score. Treatment weeks varied greatly, 3 of the 4 studies used treatments ranging from 6-8 weeks and the fourth study used a 3-week treatment program. Follow ups likewise varied between studies with 2 studies providing a 12 month follow up and 1 study with no follow up. Description of studies are summarized in Table 2.

Synthesis of Results

Based on the Open Meta-Analyst tool the Q value was 3.189 and P-value was 0.203, indicating studies assessing the subjective pain scales with either the VAS or NRS was heterogeneous. However, the I^2 = 0.38 suggests a low degree of heterogeneity, indicating the studies are predominantly homogenous. A fixed-effect model was utilized to determine the combined effect size of, (d= - .658, 95% CI [-.999, -.316]) which demonstrated CLBP interventions with PNE showed statistical significance and a moderate effect on decreasing pain in individuals with CLBP when compared to interventions alone. Results of the statistical analysis performed on the RMDQ and QBPDS exhibited a Q value of 5.939 and p-value of 0.051 indicating the studies were heterogeneous. The combined effect size of the studies showed a moderate effect size, (d = -.469, 95% CI [-1.111,0.174]) which indicates interventions with PNE has a moderate effect on decreasing functional outcome scores on the population with CLBP when compared to interventions alone. The combined effect size however, did not reach statistical significance. Effects sizes, upper and lower confidence intervals based on 95% confidence interval for pain and function are displayed in Tables 3 and 4 respectively. The data are also presented as a forest plot in Figure 2.

The forest plot for the pain outcome measure is negative, which indicates a reduction of pain intensity in individuals with CLBP when treated with PNE and an intervention. Similarly, the forest plot for the functional outcome measure is also negative, which indicates an improvement in self-perceived function when treated with PNE and an intervention. Therefore, PNE in addition to an intervention has greater reduction in pain and improvement in function when compared to interventions alone.

DISCUSSION

The purpose of this meta-analysis was to assess the effectiveness of pain neurophysiology education (PNE) with physical therapy intervention compared to physical therapy interventions alone on pain and function in individuals with chronic low back pain (CLBP). The hypothesis was PNE with physical therapy intervention will demonstrate a greater treatment effect on reducing the intensity of pain and improving function when compared to physical therapy interventions alone. The results from this meta-analysis partially accepted the null hypothesis with no statistically significant difference on function when comparing PNE with therapeutic interventions to therapeutic interventions alone. The alternative hypothesis was accepted with statistically significant improvement on decreasing pain intensity. Both groups demonstrated a positive effect, with greater effects on pain and function when physical therapy interventions were administered along with PNE. This discussion will examine the results and heterogeneous findings, provide additional literature support for biological mechanisms involved with PNE, identify limitations, and explore possibilities for future research.

Results of the Meta-Analysis

The meta-analysis demonstrated pain neurophysiology education (PNE) with physical therapy intervention had a greater effect when compared to physical therapy interventions alone in reducing the intensity of pain and improving function in individuals with chronic low back pain (CLBP). The results for pain demonstrated the effect of PNE with physical therapy intervention was statistically significant with a moderate combined effect size of – 0.658. However, a data analysis between groups exhibited a low degree of heterogeneity with an $I^2 = 38\%$. The results for function demonstrated a moderate combined effect size -0.469 in

favor of PNE with physical therapy, though the combined effect size did not reach statistical significance as 1 study favored physical therapy intervention only. Despite a moderate effect size on both pain and function, interpretation of the results must be considered with caution due to the heterogeneity demonstrated between studies. These findings require a closer examination to determine the reason for heterogeneity in pain and function.

Heterogeneity Issues

The Q statistic was used to determine heterogeneity between studies. However, due to the small number of studies included in this meta-analysis, the statistical power of the Q statistic is low.[68] Therefore, I^2 was calculated to provide the degree of heterogeneity with the pooled result. As mentioned earlier, the results for pain intensity exhibited a low degree of variability ($I^2 = 38\%$), whereas function demonstrated medium heterogeneity ($I^2 = 65\%$). These findings necessitate careful consideration for variability when examining possible contributing factors such as study characteristics, treatment duration, and variations in PNE delivery.

Study characteristics that could result in heterogeneity includes sample size and baseline characteristics. Two studies demonstrated similar within-group sample sizes and baseline characteristics, but large variation of sample sizes existed in all articles, from n = 12 to n = 80. Tellez-Garcia et al.[58] (n=12) demonstrated trigger-point dry needling with PNE had the highest effect for function when compared to other studies, and a moderate effect on pain. However, the forest plot for both pain and function exhibited a wide confidence interval, indicating increased variability and uncertainty of the data. Individuals from both groups showed similar improvements, therefore, due to the inherent variability of

a small sample sized study, it can be argued trigger point dry needling was the reason for the change. A third comparison included 2 studies with different sample sizes, Ryan et al.[56] n = 20 and Ferreira et al.[14] n = 80. These 2 studies were compared due to the inclusion of a "Back to Fitness" general exercise program which was developed by Moffett and Frost.[67] This comparison demonstrated the greatest improvement in pain in favor of PNE and exercise, however, utilization of 2 studies led to increased variabilities with baseline characteristics.

Ferreira et al.[14] demonstrated higher baseline values in 3 notable categories: Duration of pain, pain levels, and disability. Individuals from the study were considered hard to treat as they reported moderate to severe back pain which lasted greater than 3 years. Also, they were reportedly from lower socioeconomic backgrounds with a majority unemployed during the study. Whereas individuals from Ryan et al.[56] averaged 7 months of LBP with lower pain and disability ratings and no mention of socioeconomic levels. Although differences between studies appear to be significant, one could contend that individuals in Ferreira et al. accurately represents the population of individuals with CLBP, where the condition is often associated with significant economic burden, disability, and biopsychosocial factors.[2,69] Thus, utilizing the study as a control group for exercise could strengthen the meta-analysis. Along with differences in sample sizes and baseline characteristics, studies demonstrated significant standard deviations (SD) with pain and function, indicating large variability around the mean value.

As figure 3 shows, the forest plot for function with Pires et al.[57] favored aquatic physical therapy when compared to PNE and aquatic therapy. Results at the 6-week post-intervention period demonstrated both groups exceeded the minimal clinically important difference (MCID) of 5 for the Quebec Back Pain Disability Scale (QBPDS)[64]. However, despite a greater change from baseline for

PNE with aquatic therapy (-11.1) compared to aquatic therapy alone (-7.7), aquatic therapy alone exhibited a greater effect due to a lower standard deviation value. Despite individual variability in perception of pain and function, a closer examination of Pires et al. found a positive trend in favor of PNE and aquatic therapy at the 6-week post-intervention and at the 12-week follow-up. There appeared to be a positive effect with PNE based on treatment duration.

Statistical significant differences were found within-group in Pires et al.[57] for pain at 6 weeks and both outcome measures at 12 weeks in favor of PNE with aquatic therapy. Results post-intervention showed 60% of individuals with PNE perceived a MCID in pain[60,61] and function[63,64] compared to approximately 40% of the control group. The 12-week follow-up exhibited a perceived benefit for function in 72.4% of individuals with PNE compared to 44.4% in the control group. This study demonstrates that the education component of PNE appears to effectively re-conceptualize the meaning of pain in individuals, that despite their level of pain, they can move, exercise, and continue daily activities. Previous studies demonstrated similar positive relationship with changes in maladaptive beliefs in regards to performing a physical activity such as straight leg raise and lumbar flexion.[70] Several other studies have demonstrated a reduction in pain catastrophizing, fear-avoidance, and pain experience.[71,72]

In addition to the results exhibited by Pires et al., Ryan et al.[56] also showed improvements over time in pain. At the 12-week follow-up, there was a positive trend in perception of pain in favor of PNE with general exercise compared to general exercise alone. However, the results were not statistically significant. The silver lining here is regardless of the statistically insignificance, there appears to be clinical benefits to PNE. The cost-effect benefits PNE potentially provides can be appealing to physical therapists. Research has been recently increasing with

more randomized control trials. Louw et al.[73] recently completed the first 3-year follow-up of a randomized control trial that compared traditional to PNE pre-operative education for lumbar surgery. Results found no differences in patient reported outcomes for both groups, but, the PNE group demonstrated significant behavioral changes with decreased use of health care and subsequent reduction in costs. Reconceptualization of pain appears to develop self-efficacy for patients with chronic pain and improve overall quality of life. Recent systematic review deemed PNE as an effective intervention for musculoskeletal disorders in reducing pain intensity, disability, pain catastrophization, fear-avoidance, maladaptive attitudes and behaviors, limited movement and healthcare costs.[54,55] With the support of evidence and increasing amount of studies, there is a need to develop a standardized delivery for PNE.

Variability in PNE Delivery

All studies in this meta-analysis utilized the book Explain Pain (EP)[23], but the method of delivery varied based on setting, content, timing, frequency, and tools. A review of literature identified the longest PNE session was 4 hours in 1 session[24], and the shortest was 30 minutes for 1 session.[54] Studies varied between single and multiple PNE sessions, but 3 studies were identified that performed the intervention once per week.[54,56,58] The setting in which PNE was delivered was primarily face-to-face individual interactions.[24,57] According to a Louw et al., face-to-face sessions resulted in greater outcomes than group sessions.[58] Tools utilized in various PNE session include pictures, metaphors, drawings, workbooks, and power points.[74]

The largest effect on pain and function (excluding Tellez-Garcia et al.[58] due to variability) in this meta-analysis was demonstrated by Ryan et al.[56] The

experimental group received a single educational session for 2.5 hours. Contents of PNE included reshaping belief and attitudes about LBP, attempts to decrease fear and avoidance beliefs, decrease avoidance behavior, and increase self-efficacy. There was no information in regards to what media tools were used, timing of the education, and more importantly if it was a face-to-face session versus group session. For pain intensity, Pires et al.[57] exhibited a moderate effect, -0.38. The experimental group received 2 group sessions, 90 minutes each prior to beginning the aquatic therapy program. Contents of PNE were delivered by metaphors and pictures, which has been found to be favorable compared to other delivery methods.[74] Topics included acute pain origin in nervous system, transition from acute to chronic pain, centralization, role of brain in perception, cognitive behavioral, flare-up management and pacing. Overall, the 2 studies demonstrated PNE improved an individual's perception of pain. This may be due to the contents that re-conceptualized pain through beliefs, behavior, biology, and coping strategies. Due to the lack of information in regards to timing, tools, and single or group session with Ryan et al., there does not appear to be a clear advantage in PNE delivery among the studies utilized in this meta-analysis.

Biological Implications of PNE

Based on the benefits reported in literature and in this meta-analysis, it is important to discuss how PNE may biologically influence individuals in reducing the perception of pain. Moseley recently stated the biological mechanism at which PNE modulates pain has yet to be identified.[75] The pain neuromatrix, a theoretical framework used to explain an individual's perception of pain, is incorporated into pain neuroscience education to explain the multidimensional experience of chronic pain.[19,22] This theory applies to CLBP as individuals develop a unique

neurosignature comprised of neuronal networks widely distributed throughout the cortex; this is continually triggered and shaped by inputs such as sensory information, beliefs, and emotions. These inputs are then compared to previous instances of CLBP to assess the threat level of the current situation. Due to the chronicity of the symptoms, the nervous system of an individual with CLBP will often be in a hypersensitive state; the slightest input can lead to the activation of the neurosignature, and ultimately the output of pain perception, increased stress levels, and altered motor patterns. Thus, the concept of pain is not only a result of a single sensory input from injury, but rather an interaction of multiple inputs to the neurosignature that produces an output of the perception of pain.

A case study conducted by Louw et al.[76] demonstrated the activation of numerous cortical structures in relation to pain with functional magnetic resonance imaging (fMRI) scans. The individual had a history of CLBP and a current episode of LBP. Four scans were taken. The first 2 scan's established baseline cortical activity with the patient at rest. The third scan involved performing a pain provoking task, where the individual would rest for 30 seconds and then perform anterior pelvic tilt for 30 seconds. This was repeated 5 times. The fMRI produced images of widespread cortical activation during the painful task, indicating that pain does not originate from 1 structure but rather a network of structures, the pain neuromatrix. After application of a one-to-one, 30-minute PNE session, post measurements were taken with outcome measures and fMRI. Several positive changes post-PNE included a 10% decrease of the Oswestry Disability Index (ODI), 10-point decrease in the Pain Catastrophizing Scale (PCS), improved straight leg raise (SLR) by 7 degrees, and improvement in beliefs and attitudes regarding the upcoming surgery. The fMRI was conducted post-PNE and demonstrated significant decreases in the activation of cortical structures, which

correlated with her subjective reports of less discomfort compared to baseline. Conclusions from this study demonstrates the importance of PNE in creating positive changes with various cortical structures (pain neuromatrix) in relation to cognition, beliefs, and perception of pain.

The use of fMRI in real-time analysis of cortical structures with pain and effects of PNE is fairly new, therefore results of the case study should be taken with caution. However, literature supports differences in cortical structures that occur in individuals with chronic pain. Several key structures such as the dorsolateral prefrontal cortex (DLPFC), limbic system, and anterior cingulate cortex (ACC) may be more involved than others.[77,78]Apkarian et al. compared brain morphology between 26 individuals with CLBP to those without pain and found the group with CLBP exhibited 5-11% less gray matter volume in the bilateral dorsal prefrontal cortex and right thalamus.[79] He implies the results may be related to pain characteristics unique to individuals with chronic pain. Lorenz et al. supports that connections from the DLPFC, thalamus, and midbrain are involved in pain modulation.[80] He suggested prefrontal cortical thinning and subsequent decreased activation of the left DLPFC can lead to a decreased ability to regulate emotions. This can be observed in individuals with CLBP as they often exhibit anxiety, fear avoidance behaviors, or catastrophization.[71,72]

The amygdala is known for the perceptions of emotions such as anger, fear, and sadness. Toyoda et al. states that in addition to the amygdala, the ACC, prefrontal cortex, and hippocampus may also contribute to the development and processing of fear memory.[81] He further explains the expression of fear involves the activation of the amygdala to identify danger signals while the ACC establishes neural activity to sustain attention to the threat level. Fear is an adaptive response to threat, or in the case of this meta-analysis, the threat of

CLBP. Individuals suffering from CLBP can be conditioned by fear, forming negative neuroplasticity between the amygdala and hippocampus that can potentiate overtime. The synaptic pathways that form due to the conditioning of fear in the prefrontal cortex, ACC, and limbic systems shift the persistent nociceptive input to more of an emotional distress.[82]

With heightened emotions and physical stress, a hormonal response can occur. The hypothalamic-pituitary-adrenocortical (HPA) axis is a proposed biological mechanism in which chronic stress can affect an individual's well-being.[83] The release of cortisol influences the CNS (emotion, learning, and memory), immune system (regulating inflammatory responses), and metabolic system (regulating glucose levels). Overtime, chronic exposure can lead to depression, obesity, tissue damage, and dysregulation of multiple body systems. Although Mosely states there is no clear biological explanation of pain, the studies above provide insights into the possibility between structures within the neuromatrix.[75] The interactions of all these implicated structures can possibility perpetuate the endless cycle of pain and hypersensitivity many people with CLBP have. Ultimately, PNE is a psychosocial approach to physical therapy that seeks to target these hyperactive structures and rewire the neuromatrix to a level where they can function and quality of life.

Clinical Implications

The high-quality randomized controlled studies included in this meta-analysis have shown PNE has a therapeutic effect in decreasing the perception of pain. Systematic reviews and other randomized controlled trials have demonstrated PNE is also effective in decreasing disability, catastrophization, and the use of healthcare.[54,55] Although evidence continues to develop for the use of

PNE, there is a paucity of information about the clinical applications of PNE. Studies presented in this meta-analysis alone provided different methods of delivering PNE. Ultimately, the efficacy of PNE is individualized due to the multidimensional aspects of pain. However, Louw et al.[84] compiled studies to identify key elements that can help guide clinicians with the use of PNE. These elements include: examination, content, delivery methods, and including various interventions.

As with all physical therapy examinations, it is important to rule out red flags and determine what is relevant to the individual's issue. Individuals with chronic pain can present with somatic or neuropathic pain in addition to chronic pain, therefore carefully listening and performing appropriate test and measures will be necessary. Developing rapport is significantly important; as many of the individuals with chronic pain may have visited many health care practitioners and interpret that the care received was inadequate care for their issues. Fostering trust and confidence can help the individual be more receptive to PNE. If PNE is indicated, an introduction to pain can be provided to the individual during the examination. According to Gallagher et al.,[74] PNE is more effective with metaphors, examples, and pictures when explaining the complexities of the nervous system.

Practitioners will likely need to practice the skill of delivering PNE to develop confidence and improve effectiveness. Also, due to the individualized experience of pain, they may benefit from different topics of PNE. However, a standardized approach may be more beneficial when developing randomized control trials. Studies have demonstrated varying amount of time required to deliver. In an outpatient clinic, each visit can incorporate a topic that would benefit the patient with metaphors in 10 minutes.[84] This meta-analysis

demonstrated PNE with an intervention is more effective at decreasing pain then interventions alone, therefore it would be important to use PNE in adjunct to various treatments as well as HEP.

Individuals with chronic pain seek healthcare practitioners because they want to know about the pain. Though the traditional biomedical model is useful in addressing acute pain, however the benefits are variable with chronic pain. PNE appears to be an effective approach, but research needs to continue developing studies to identify optimal methods for clinical application.

Limitations and Future Research

The amount of heterogeneity between these studies serve as a limitation in this meta-analysis. This could be due to a variety of factors. The differences in sample sizes which ranged from 12-80, and small number of studies warrants caution when interpreting the results of the studies.[14,58] The duration of follow-ups can also be a limiting factor. Pires et al.[57] demonstrated that improvements in both pain and function can continue to occur over a 12-week period. Also, the delivery of PNE is highly variable among the studies presented in this meta-analysis. Standardization of study design, subgrouping individuals with LBP, and outcome measure can lead to stronger meta-analysis and systematic reviews for the effectiveness of PNE.

Despite the numerous treatments available for CLBP, the incidence has continually increased within the last 2 decades.[1] Future studies are needed to decrease socioeconomic burden in society and improve the quality of life for individuals with CLBP.[2] Based on the limitations, improving a methodological approach can lead to a better understanding of the efficacy of PNE and its clinical implications. Also, identifying the difference of effectiveness between one-to-one

and group sessions can have beneficial implications for cost-effectiveness. If the outcomes for both approaches are similarly effective in improving pain and function, then both clinicians and individuals may benefit from a group session due to issues with time constraints and insurance.

Lastly, identifying the effectiveness between PNE with 1 physical therapy intervention compared to another can help clinicians utilize the best clinical approach for individuals with CLBP. Due to the continual improvements of PNE with aquatic therapy, it may benefit researchers to explore different frequency and durations of aquatic therapy to identify an optimal program.[57] The buoyancy effects of aquatic therapy and continual sensory pressure to individuals with CLBP may be an excellent adjunct to PNE. Reconceptualizing pain within the CNS with education while simultaneously decreasing the threat level through the aquatic environment can be explain the continual improvement in Pires et al.[57]

Conclusion

Pain neurophysiology education with physical therapy interventions has been shown to be more effective in decreasing the intensity of pain in individuals with CLBP than with physical therapy interventions alone. However, the effects of PNE and physical therapy interventions on function was not statistically significant, but demonstrates clinical significance. Overall, PNE should be used in adjunct to other physical therapy interventions due to the relative ease and benefits found in reducing the perception of pain.

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TABLES

Table 1. Results of Individual Studies

Criterion	Meta-analysis			
	Pires et al.[15]	Tellez-Garcia et al.[58]	Ryan et al.[56]	Ferreira et al.[14]
1. Random allocation of subjects	√	√	√	√
2. Allocation concealment	√	√	√	√
3. Similar groups at baseline	√	√	√	√
4. Subjects blinded	√	√	√	√
5. Therapists administering treatment blinded				
6. Assessors blinded				
7. One key outcome obtained from 85% of subjects initially allocated to groups	√	√	√	√
8. 'Intention to treat' used for analysis of one key outcome	√	√	√	√
9. Between-group statistics for one key outcome reported	√	√	√	√
10. Point measures and measures of variability for one key outcome	√	√	√	√
Total score	8/10	8/10	8/10	8/10

Table 2. Study Characteristics for Meta-Analysis

Study	Subjects	Inclusion Criteria	Experiment	Control	Outcome measures	Follow-up
Pires et al.[57]	With PNE - n = 30 (20F) - Age = 50.9 (6.2) Control - n = 32 (20F) - Age = 51 (6.3)	LBP for at least 3 months, with or without pain referred to the leg, aged 18-65	1. PNE: 2 group sessions, 90 min each. 2. Topics: - Acute pain origin in nervous system - Transition from acute to chronic pain - Central sensitization - Role of brain in perception - Cognitive and behavioral responses related to pain - flare-up management and pacing - metaphors and pictures used throughout the session 3. Aquatic program: 6 weeks, 2x/week	1. 6-week program consisting of 12 session of aquatic exercise. - Groups of 6-9 - 30-50 minutes - 3 phases: warm-up, specific exercise, warm-down	1. VAS M: 20.6 SD: 19 2. QBPDS M: 27.6 SD:17.2	12 weeks
Tellez-Garcia et al.[58]	With PNE - n = 6 (4F) - Age = 37 (13) - CLBP (months) 19 +/- 8 Control - n = 6 (4F) - Age = 36(5) - CLBP (months) 17 +/- 9	CLBP individuals referred by their physicians, sx localized below costal margin and above gluteus area, > or = to 3 months, aged 18-65, without pain referred to the leg for > 1 year, score > or = to 4 points on RMDQ, have not received PT within the last 6 months, and exhibits at least 1 active Trp reproducing their sx	1. PNE: 2 individual, face-to-face sessions, 30 min each. 2nd/3rd week of the study. After TrP-DN. 2. Topics: - No reference to L/S - Informed on role of beliefs and attitudes toward their pain - PPT presentation based on EP - During session, pts were encouraged to ask individualized questions - Homework about pain physiology concepts 3. Trp-DN 3 weeks, 1x/week	1. 3 weeks, 1x/week 2. Active TrPs located in the gluteus medius and quadratus lumborum muscles were treated with TrP-DN. All patients received 3 sessions of TrP-DN over active TrPs 1x/week.	1. NRS M: 1.2 SD:1.1 2. RMDQ M: 2.2 SD: 0.8	1 week
Ryan et al. [56]	n = 20 - 14F - Age 45.2 (11.9) - CLBP (months) 7.6 +/- 7	CLBP individuals with non-specific LBP > 3 months, aged 18-65	1. PNE: 1x 2.5 hr session 2. Topics - Reshaping pt's belief and attitudes about their back pain - Attempt to decrease fear and avoidance beliefs and harm beliefs - Increase self-efficacy - Decrease avoidance behavior 3. "Back to Fitness exercise class" - 6 weeks, 1x/week - circuit-based, graded, aerobic exercises with some core stability exercises. - 3 phases: warm up (10 min), aerobic (20-30 min), warm-down (10-15 min) 4. Aerobic phase involved circuit based with easy, moderate, and hard version. The pt can choose which version to perform.		1. NRS M:23.9 SD: 23.3 2. RMDQ M: 5.6 SD: 3.9	8 weeks 12 weeks

Table 2 (cont.)

Study	Subjects	Inclusion Criteria	Experiment	Control	Outcome measures	Follow-up
Ferreira et al.[14]	n = 80 - 56F - Age 54.8 (15.3) CLBP (months) - 17 pts (3-12) - 11 pts (13-36) - 52 pts (>36)	Non-specific LBP for > 3 months, aged 18-80, and provided written informed voluntary consent		1. 8 weeks, 12 treatment sessions - 1 hour classes, 8 people per class - intensity progressed over 12 sessions - "Back to fitness exercise class" - Program included strengthening and stretching exercises for main muscle groups. - 3 Phases: warm up, 10 exercies performed 1 min each, warm-down session. - After warm-down, there was a relaxation session with a brief educational message. - At the 12th session, pts discussed what new activity they had adopted and how they plan to maintain it.	1. VAS M: 4.8 SD: 2.4 2. RMDQ M: 9.7 SD: 6.3	8 week 24 weeks 52 weeks

Table 3. Effect Size and Confidence Interval for Pain

Study	Effect Size	CI Upper	CI lower
Pires et al.[57]	-0.382	-0.885	0.121
Tellez-Garcia et al.[58]	-0.351	-1.491	0.789
Ryan et al.[56] and Ferreira et al.[14]	-1.002	-1.511	-0.493
Total ES	-0.658	-0.999	-0.316
Fixed effect		No change	

Table 4. Effect Size and Confidence Interval for Function

Study	Effect Size	CI Upper	CI lower
Pires et al.[57]	0.056	-0.442	0.554
Tellez-Garcia et al.[58]	-1.151	-2.373	0.070
Ryan et al.[56] and Ferreira et al.[14]	-0.688	-1.187	-0.189
Total ES	-0.469	-1.111	0.174

FIGURES

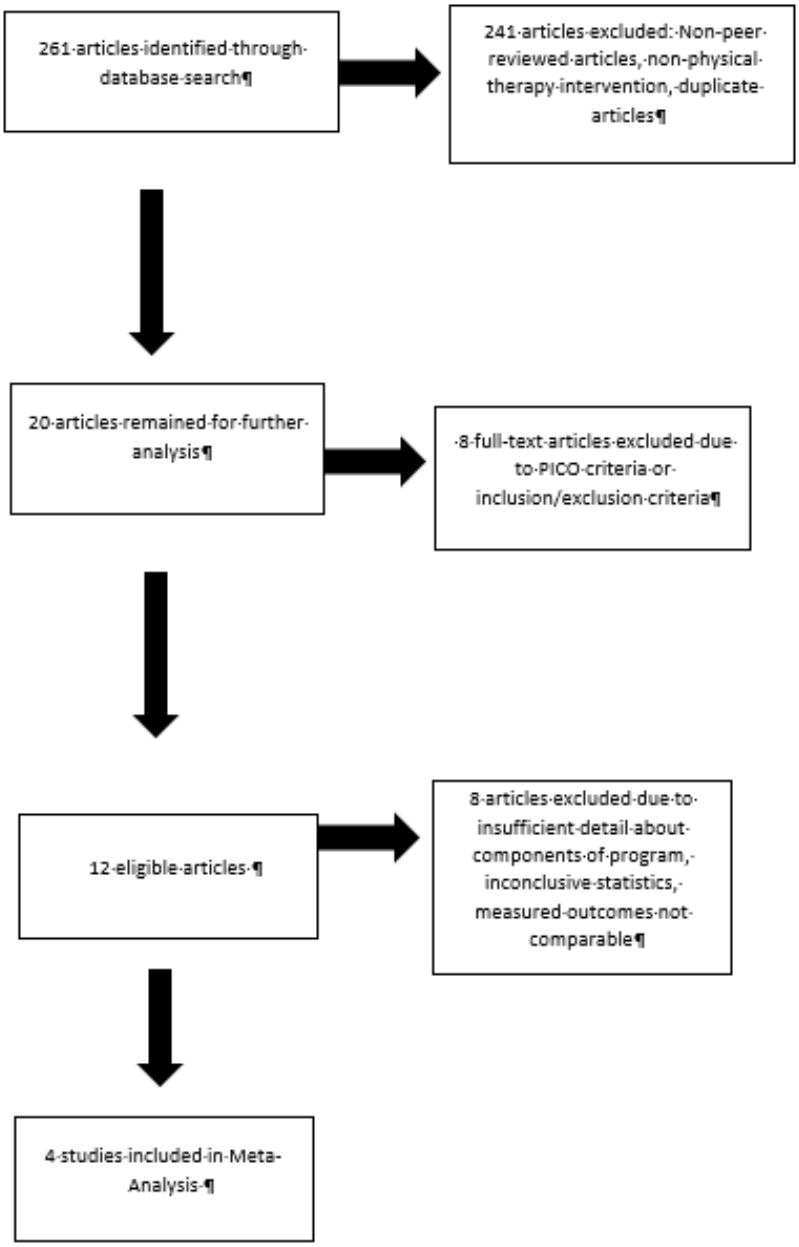

Figure 1. Consort

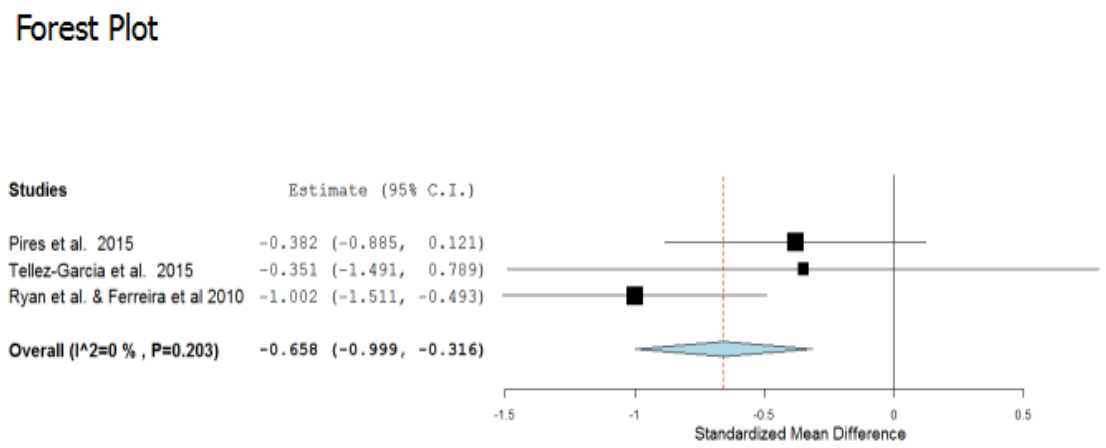

Figure 2. Forest plot on the effect of PNE with intervention compared to intervention alone on pain between groups

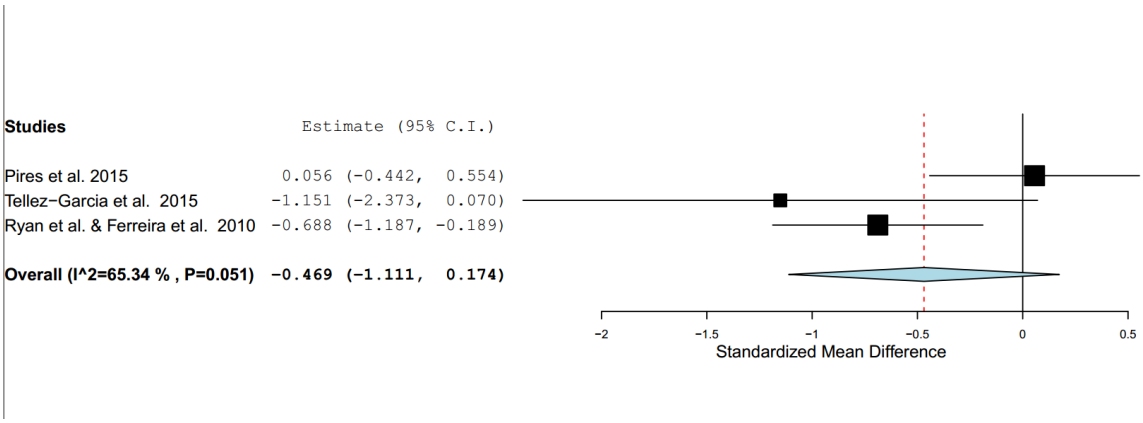

Figure 3. Forest plot on the effect of PNE with intervention compared to intervention alone on function between groups.