ABSTRACT

PAIN NEUROPHYSIOLOGY EDUCATION IN CONJUNCTION WITH TREATMENT INTERVENTIONS DECREASES CHRONIC LOW BACK PAIN MORE THAN TREATMENT INTERVENTIONS ALONE: A META-ANALYSIS

Back pain has been ranked sixth in overall national medical costs[1] and second most common reason Americans utilize physician visits.[2] More than 30% of U.S. adults report experiencing back pain in the previous 3 months[2,3] and approximately half of the 30% will develop chronic low back pain (CLBP), contributing to annual care expenses of $84.1-$624.8 billion. Current physical therapy practice guidelines for low back pain are varied and none address all pain that CLBP patients are suffering beyond normal tissue healing and are experiencing an abnormal increase in the body's natural pain alarm system.[7,13,17,18,30-37] Studies show that Pain Neurophysiology Education (PNE) can improve the pain alarm system making an important element that should be included in clinical practice guidelines.[37-52] An electronic search was performed covering the years 2000-2017 from the following databases: CINAL, PubMed, and APTA JOSPT. The search strategy yielded 113 articles, after duplicates were removed, inclusion criteria and exclusion criteria met, 2 articles remained. The pain analysis demonstrated homogeneity ($Q= 2.38$, $p= 0.34$) of the articles[64], had a low total variation ($I^2= 15.97\%$).[65]The overall effect size ($d= -.21$, 95% CI [-.53, .12]).[64] The current biomedical education is not working, which is clearly reflected in the CLBP epidemic. PNE has shown to diminish psychosocial factors during medical visits[20,31,54,55] and has a small effect on reducing CLBP, making it a logical substitution to the current biomedical education.

Kelley Urionaguena
May 2018

PAIN NEUROPHYSIOLOGY EDUCATION IN CONJUNCTION WITH TREATMENT INTERVENTIONS DECREASES CHRONIC LOW BACK PAIN MORE THAN TREATMENT INTERVENTIONS ALONE: A META-ANALYSIS

by

Kelley Urionaguena

A project

submitted in partial

fulfillment of the requirements for the degree of

Doctor of Physical Therapy

in the Department of Physical Therapy

College of Health and Human Services

California State University, Fresno

May 2018

APPROVED

For the Department of Physical Therapy:

We, the undersigned, certify that the project of the following student meets the required standards of scholarship, format, and style of the university and the student's graduate degree program for the awarding of the doctoral degree.

Kelley Urionaguena
Project Author

Nupur Hajela (Chair) Physical Therapy

Monica Rivera Physical Therapy

For the University Graduate Committee:

Dean, Division of Graduate Studies

AUTHORIZATION FOR REPRODUCTION

OF DOCTORAL PROJECT

X I grant permission for the reproduction of this project in part or in its entirety without further authorization from me, on the condition that the person or agency requesting reproduction absorbs the cost and provides proper acknowledgment of authorship.

_____ Permission to reproduce this project in part or in its entirety must be obtained from me.

Signature of project author:_____

ACKNOWLEDGMENTS

To my hairy child Barley, thanks for all the oxytocin and the reminders to make time to live. I promise we will now play more ball.

TABLE OF CONTENTS

Page

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

BACKGROUND

Back pain has been ranked sixth in overall national medical costs[1] and second most common reason Americans utilize physician visits.[2] More than 30% of U.S. adults report experiencing back pain in the previous 3 months[2,3] and approximately half of the 30% will develop chronic low back pain (CLBP), contributing to both direct and indirect annual care expenses of $84.1-$624.8 billion.[1,2] Back pain is a common ailment in the American lifestyle and will be experienced at least once in the lifetime of every individual[4-6] and 60-70% of low back pain episodes are of an idiopathic nature.[7] This is alarming, as any pain experience causes vulnerability and change to the body and mind at any age or stage of life.[2,4,6,8] Pain typically occurs in brief episodes that cease with healing but, it can persist beyond typical tissue healing of 3 months and progress into a disease process known as chronic pain.[1,4,9] Chronic pain reduces quality of life and necessitates the use of medical care, narcotics, and sick leave.[1,2,4-6,8,10]

This information presents the economic burden of CLBP that imposes societal hardships through lost household productivity, early retirement, and health vulnerability with inactivity.[1] However, studies show that there are modifiable risk factors that promote the advancement of pain from acute to chronic.[4,5,9,11-15] The early recognition of patients with higher risk will not only help control these costs, but could alleviate suffering for many Americans.

Psychosocial Factors and Chronic Pain

The identification of patients who are susceptible to the development of chronic pain can be done with an assessment for psychosocial risk factors, referred to as yellow flags.[12,15,16] These warning signs are rooted in psychosocial conditions such as anxiety, depression, and distress, which are often displayed by patients

when progressing from acute to chronic pain. [9,12,14,17-19] Other major contributing psychosocial processes that also increase the likelihood of developing chronic pain are fear-avoidance behaviors, post-traumatic stress syndrome, decreased perceived social support, pain catastrophizing, and low self-efficacy.[9,11,14,17-24] The treatment of these patients requires more than simple pathoanatomic corrections, but rather a biopsychosocial approach that addresses the emotional aspect of pain.[9,11,14,15,17,18,25] Current treatment guidelines are ambiguous when it comes to CLBP and there is no information on how to address psychosocial issues that are the basis of chronic pain.[25]

Clinical Practice Guidelines for Chronic ow Back Pain

There have been many attempts to create a comprehensive clinical practice guideline to define the most effective treatment for CLBP.[3,26-29] The challenge of making these guidelines comes from trying to categorize patients with significantly diverse etiologies, wide age ranges, different levels of functional limitation, length of disease progression, and contribution of variant psychosocial factors into a few succinct groups to be given specific treatment.[4-6,8] Despite the vast variation in CLBP etiologies and other major factors many patients receive the same relative treatments.[15,27]

Current physical therapy practice guidelines for both acute and chronic low back pain interventions recommend: mobilizations and manipulations, trunk strengthening, coordination, and endurance exercises, repeated movements to promote centralization of symptoms, moderate to high intensity exercises, and the use of patient education and counseling.[3,26-29] None of these interventions address all pain that CLBP patients are suffering beyond normal tissue healing and are experiencing as an abnormal increase in the body's natural pain alarm

system.[7,13,17,18,30-37] Studies show that Pain Neurophysiology Education (PNE) can improve the pain alarm system by teaching patients about the biological and psychological pain process, making it an important element that should be included in clinical practice guidelines. [37-52]

Pain Neurophysiology Education

PNE is a biopsychosocial educational approach that targets three interactive systems that collectively contribute to chronic pain: biology, psychology, and sociology.[11,30-32,53] This differs from typical biomedical education, which utilizes anatomical information and other biomechanical disorders or dysfunctions as the root cause chronic pain.[30,31,38-40] PNE also differs from cognitive behavioral therapy, as it is not a specific set of procedures or techniques, but rather an educational conversation targeted at the individual to alter the understanding of the purpose of pain and the biological science from which it is created.[30,31,38] PNE also emphasizes that nociception, which is the transmission of a noxious sensation, does not always mean pain will occur and moreover that pain can be perceived without nociception transmission.[7,17,18,31,32,36-38,50] This means that pain is only evoked if the sensory input reaches a harming level, causing a danger message to be sent to the brain, and the brain ultimately decides if the situation requires action for protection.[13,30-32] Additionally, pain can be felt when anticipated by the brain; as demonstrated in studies where subjects are told a stimulus would be painful, when in fact it was something benign.[7,31,32,37] So it is not surprising to state that the areas in the brain that are involved in the cognitive aspect and response to pain, the mesolimbic-prefrontal areas, are the same areas that control behavior responses such as: fear, aversive conditioning, attention, motivation/engagement/ disengagement, and executive control.[7,17,18,31,32,35-37] When something goes wrong

with either the central or peripheral protective biological mechanisms it can lead to the semi-permanent adaptations in both areas, meaning both collectively contribute to chronic pain.[30-32]

Therefore, the biological aspect of pain can be affected by psychosocial conditions; meaning how a person emotionally processes pain can contribute to its severity and duration through alterations in the organisms in the periphery and brain.[11,30-32] Furthermore, thoughts and beliefs about pain also have the power to initiate other response systems of the body: the autonomic nervous system, endocrine responses, and the immune system resulting a heightened state of protection in the body while the systems are activated.[31,32] Studies have also shown that a negative emotional state of a patient can be created or heightened through the use of words or phrases of medical terminology, diagnoses, or jargon that suggest fragility or unrepairable condition of a body part; which are common components of the biomedical education.[20,31,54,55] PNE recognizes that pain is unique to the individual and influenced by thoughts and beliefs, reduces the use of pain evoking medical terminology, and gives patients the knowledge to process painful circumstances.[17,18,30,31,34,35,37]

Physical Therapy and Pain Neurophysiology Education

Few studies have been conducted and only 1 meta-analysis has been performed reviewing the effect of PNE on decreasing pain and increasing function of prevalent CLBP patients versus usual treatment provided by physical therapists based on recommended interventions. The purpose of this paper is to compile the limited evidence for greater power to determine if patients who receive PNE along with recommended physical therapy treatment described in clinical practice guidelines, will have greater improvements on pain than when physical therapy is

used alone. The relevance is to provide clinical treatment evidence for the only characteristic of all CLBP patients for future clinical practice guidelines and help determine if a biopsychosocial approach is more appropriate for patients who are experiencing chronic pain.

METHODS

Eligibility Criteria

Articles of level 1 or 2 evidence would be extracted based on the PICO: *population:* men and women, aged 18-65, CLBP greater than 3 months, *intervention:* PNE with or without usual physical therapy treatment, *comparison:* usual physical therapy treatment for CLBP that can include other forms of education that do not encompass PNE, *outcomes:* a pain scale and a function scale.

Search Strategy

An electronic search was performed covering the years 2000-2017 from the following databases: CINAL, PubMed, and APTA JOSPT. All variables that were selected during the search included: English articles, peer reviewed journals, research articles, and full text. Search terms included: patient education or patient teaching AND catastrophizing AND low back pain or lumbar pain or lumbar spine pain or non-specific low back pain// pain education AND low back pain or lumbar pain or lumbar spine pain or non-specific low back pain// neurophysiological education AND catastrophizing AND low back pain or lumbar pain or lumbar spine pain or non-specific low back pain// neurophysiological education AND low back pain or lumbar pain or lumbar spine pain or non-specific low back pain// pain education AND low back pain or lumbar pain or lumbar spine pain or non-specific low back pain NOT exercise// “pain neurophysiology education”// “pain neurophysiology” AND low back pain or lumbar pain or lumbar spine pain or non-specific low back pain//

Study Selection

Eligibility assessment was performed independently and unblinded by 1 reviewer, KU, to determine the inclusion of the article for the systematic review and meta-analysis.

Inclusion Criteria

All titles and abstracts were reviewed for inclusion of a biopsychosocial model of physical therapy that included PNE for CLBP patients. When accepted, a full text version of the article was read to ensure it met criteria of: low back pain 3 months or greater, men and women subjects ages 18-65, outcome measures of pain and function, intervention given by physical therapist, PNE was only given in the intervention group, and PNE was compared to usual physical therapy care. Additionally, usual physical therapy care is defined by current clinical practice guidelines for treatment interventions for CLBP. The PNE delivered in each of the studies was based off of the book, Explain Pain, written by Butler, D.S. and Moseley, G.L.[31]

Exclusion Criteria

Articles were excluded if they were not printed in English, were level of evidence less than 2, pain other than the low back or less than 3 months, the patients underwent surgery, the intervention did not include PNE, the control included PNE, or the control used physical therapy treatment methods not included in clinical practice guidelines.

Planned Analysis

Statistical analysis will be performed by extracting means, number of participants, and standard deviations to calculate an effect size for each study. A grand effect size will be calculated based upon a weighted effect size to determine

if the treatment effect will be greater for the intervention versus the alternate intervention. Additionally, the Q statistic will demonstrate heterogeneity or homogeneity making the Q value the deciding factor on whether to use a random or fixed effects model.

RESULTS

The search strategy yielded 113 articles, after duplicates were removed, that met inclusion criteria based on subjects with chronic low back pain and use of a biopsychosocial education intervention. Respectively, 59 articles from CINAL, 45 from APTA JOSPT and 9 from PubMed. The methods were read to assess included participants, intervention and control group procedures, and outcome measures causing 65 articles to be excluded for reasons: assessment of non-chronic pain, non-low back pain, and no use of a biopsychosocial education method. The 48 remaining articles were further processed and 30 were removed as they were not or did not contain randomized control trials, did not use standard physical therapy intervention in the comparison, patients underwent surgical intervention, or the article did not produce a quantitative assessment. This left 16 randomized control trials and 2 systematic reviews for full-text reading. The articles of the systematic reviews were individually examined and duplicates of the remaining 16 randomized control trials were removed. Additionally, 14 randomized control trials, 1 compete systematic review, and 1 article from a systematic review were excluded as they did not include an equitable amount of men and women subjects or PNE was not used specifically as the biopsychosocial method of education. The final result was 2 individual randomized control trials and 1 randomized control trial originally included in a systematic review; for a total of 3 articles that met all established eligibility criteria set by the guidelines of this meta-analysis. The 3 included articles were from authors: Moseley et al.,[45] Pires et al.,[47] and Walti et al.[49] A consort map of the included and excluded articles is listed in **Figure 1**.

Critical Appraisal

Hierarchy of Evidence

All articles included in this systematic review and meta-analysis are randomized control trials as specified by the inclusion criteria. Therefore, the articles are of level 1 or level 2 evidence, allowing data to demonstrate clinically important results.[56] Level 1 data are described as high quality randomized control trial with easily interpreted results and level 2 data are low quality randomized control trials with unclear results.[56]

Methodological quality

The quality of the research in the randomized control trials was assessed using the 11 points of criterion given on the PEDro scale[57,58] (Appendix). The study quality was not part of the inclusion criterion and was done retrospectively after the articles were identified. All the included studies have been rated to be high quality with scores: 6 of 10 Moseley et al., 8 of 10 Pires et al., and 8 of 10 Walti et al.[57,58] All 3 articles failed to blind the subjects and the therapists, allowing for potential biases in the data.[57,58] However, both Pires et al. and Walti et al. used blinded assessors that were not involved in the treatment to reduce bias.[57,58] Moseley et al. did not used blinded assessors and did not run an intention to treat analysis, both ensuing to the lower quality score. The summary of each article assessment, along with criterion, is listed in **Table 1**.

Study Characteristics

The 3 articles included in this meta-analysis met the inclusion and exclusion criteria based on population, intervention, control comparison, and outcome measures. Each of the studies have a population with similar baseline characteristics of low back pain lasting 3 months or greater, men and women

subjects, and age ranges of 18-65. PNE is included in each of the interventions, but not in the control groups. Moseley et al. examined the effects of PNE alone and in comparison to biomedical education alone.[45] Pires et al.[47] and Walti et al.[49] both analyzed the effect of PNE in conjunction with other physical therapy interventions and compared the effect to just physical therapy interventions. For this meta-analysis, only the measures yielding pain and function data were extracted. A full summary of the characteristics is listed in **Table 2**.

Moseley et al. administered PNE or standard biomedical education in a 3-hour 1-on-1 session with no other intervention but additional educational material that could be read at home.[45] The PNE included diagrams and hypothetical examples involving how the nervous system, synapses, and plasticity of the nervous system can contribute to pain.[45] The control group received biomedical education that encompassed anatomy and physiology of joints, muscles, and spinal cord/nerve roots of the lumbar spine and trunk.[45] Control patients also received instruction on joint forces, lifting mechanics, fitness, and ergonomics.[45] Prior to the educational sessions, the subjects were given a Visual Analogue Scale (VAS) to quantify pain level [59] and Roland Morris Disability Index (RMDQ) to demonstrate functional limitations.[60,61] These measures were re-examined after 15 days and denoted minimum clinically important differences on both the VAS (20 mm reduction)[59] and RMDQ (2 point score reduction)[61] for the PNE group and only on the VAS[59] for the control.

Pires et al. evaluated the effects of 6-weeks of aquatic physical therapy and PNE versus aquatic physical therapy alone.[47] Both the intervention and control group received biweekly treatments of aquatic physical therapy for 30-50 minutes that consisted of warm-up, exercises, and warm-down.[47] PNE was administered to the intervention group in 2 sessions of 90-minutes prior to starting the aquatic

program and consisted of information on acute pain, central sensitization, the role of the brain during pain, psychosocial factors contributing to pain, cognitive and behavioral responses to pain, graded exercise exposure, and flare-up management.[47] At the beginning of the study, subjects were given the Quebec Back Pain Disability Scale (QBPDS) to measure functional disability [62] and the VAS to quantify pain.[59] The outcome measures were repeated at a 6-week and 3-month follow up. There was no statistical difference between the PNE and control group for pain or function at the 6-week follow up, but the 3-month testing demonstrated significant reduction in pain intensity in the PNE group over the control.[47] Additionally, more members of the PNE group consistently demonstrated scores of minimum clinical importance difference in the direction of improvement of function and reduction of pain, than members of the control group.[47] This functional difference was significant in the PNE group at the 3-month follow-up of the QBPSS.[47]

Walti et al. compared the effect of PNE, sensory retraining, motor retraining, and physical therapy to physical therapy alone.[49] Each of the groups attended physical therapy sessions 1 to 2 times a week for total of 8 weeks and a maximum of 16 visits.[49] The subjects were also given a 30-minute home exercise program and online support was given 5 days a week.[49] The intervention group received PNE in 2 to 4 sessions and were encouraged to read the Explain Pain book.[49] The intervention group also received sensory and motor retraining that was administered in the same 2 to 4 sessions of PNE.[49] The control group was given education on how to behave during a low back pain exacerbation during the physical therapy visits.[49] Before the first treatment was given, the subjects filled out the RMDQ to measure functional limitations [61,63] and verbally expressed pain level via the Numeric Rating Scale (NRS).[63] At 6-months, the outcome measures

were re-assessed and there was a significant reduction of pain in the PNE group over the control, but the reduction was not large enough to meet minimum clinical important difference.[49] There was no significant difference between the groups for the RMDQ.[49]

Results of Individual Studies

The individual studies show minor effect in favor of PNE versus control groups receiving biomedical treatment. Specifically, Moseley et al.[45] (d= -.27, 95% CI [-.78, .25]) and Pires et al.[47] (d= -.39, 95% CI [-.89, .12]) show a reduction in pain after PNE, but not Walti et al.[49] (d= .32, 95% CI [-.44, 1.08]) which demonstrates the effect in the opposite direction. The PNE intervention group demonstrated a moderate effect at improving functional abilities in Moseley et al.[45] (d= -.67, 95% CI [-1.20, -0.14]). However, this trend was not demonstrated in the other two articles with Pires et al.[47] (d= .06, 95% CI [-.44, .55]) and Walti et al.[49] (d= .78, 95% CI [.00, 1.57]) yielding results in favor of the control. The results of each study are further detailed in **Table 3 and Table 4**.

Synthesis of Results

Pain Analysis

A chi-square test was used for homogeneity and random effect for 2 groups calculation was used to test for overall effect size of the studies used in this meta-analysis. This analysis demonstrated homogeneity (Q= 2.38, p= 0.34) of the articles[64], allowing for further analysis using fixed effect for 2 groups calculation yielding the same data, **Table 3**. Additionally, the studies had a low percentage of observed total variation showing low level of real heterogeneity (I^2= 15.97%),[65] **Table 3.** The overall effect size (d= -.21, 95% CI [-.53, .12]) is small[64], but shows

a trend toward the reduction of pain and is summarized in **Table 3**. A visual depiction is represented as a forest plot of the effect size of each study and total effect size is available in **Figure 2**. In the plot, Moseley et al.,[45] Pires et al.,[47] and Walti et al.[49] cross the line of null effect and thus there is no statistical difference between the intervention and control groups.[64] Additionally, Walti et al.[49] has a wide line indicative of the small amount of subjects used in the study (95% CI [-.44, 1.08]).[64] The bottom line of the plot represents the combined results of the individual studies; it does cross the line of null effect denoting no effect[64] but falls more to left of the null effect line in favor of the PNE group.

Function Analysis

A chi-square test was used for homogeneity and a random effect for 2 groups calculation was used for overall effect size of the studies used in this meta-analysis. The functional data did not show homogeneity, but rather heterogeneity (Q= 9.66, p= 0.008), meaning that the articles are too dissimilar for an appropriate comparison.[64] Additionally, the studies show a large percent of observed total variation or real heterogeneity (I^2= 2,322%),[65] **Table 4.** The overall effect size (d= -.09, 95% CI [-.42, 24]) is negligible[64] and is summarized in **Table 4**. A visual representation is demonstrated as a forest plot of the effect size of each article and the overall effect size is in **Figure 3**. In the plot, Pires et al.[47] crosses the line of null effect demonstrating no statistical significance between the intervention and control groups.[64] The data for Moseley et al.[45] lies to the left of the null effect line in favor of the PNE group, conversely Walti et al.[49] lies to the right of the null effect line in favor of the control group. Again, Walti et al.[49] has a wide line denoting the limited amount of subjects[64] (95% CI [0.00, 1.57]). Lastly, the

combined results line crosses the null effect line showing no statistical differences between the treatment groups and no effect.[64]

DISCUSSION

Summary

Pain is used as a method of protection from immediate danger, but once the danger has passed, such as healing of tissue, then the pain alarm should be turned off.[7,17,18,30-34,37] Persistent pain occurs, because the body continues to remain in a heighten sense of protection and can no longer recognize when the body is out of danger and turn off the pain alarm.[7,13,17,18,30-34,37] PNE can help reverse the negative consequences of a malfunctioning pain alarm system**,** as suggested in the results of this meta-analysis. Although there are few studies in this analysis, the quality of the available studies is high, **Table 1**, based on the PEDro scale,[57,58] making the data more persuasive. This analysis displays that when PNE is delivered alone or in conjunction with physical therapy interventions defined by clinical practice guidelines, it has a small effect on reducing pain and no effect on improving function, in CLBP patients. These results support the alternate hypothesis of this paper. Further examination of the physiologic process of chronic pain and the contribution of the brain, can help explain why pain decreased, yet function did not increase when PNE was delivered. First, the importance of the results needs to be discussed in detail to expose characteristics of PNE and current practice guideline treatments that can be compounded to build a better protocol for CLBP patients.

This analysis demonstrated an overall small effect size, in favor of PNE reducing pain in CLBP patients, **Table 3**. Although this effect is small, the change in pain is vast to CLBP sufferers. It can be noted that this small effect occurred after one session of PNE administered alone, in Moseley et al.[45] This is a remarkable feat for patients who have been experiencing CLBP for 3 months or

more; 1 session initiated a decrease in pain and denotes the alterations that PNE can make with its implementation into treatment sessions. Additionally, the largest effect size for pain reduction in this meta-analysis, **Table 3**, occurred when PNE was provided in conjunction to physical exercise, as demonstrated in Pires et al.[47] This conveys that the summation of PNE and physical exercise interventions, easily applied in physical therapy sessions, can cause greater reductions in the pain symptomology of CLBP patients. More significantly, the data in this analysis establishes that only 1 PNE session is needed to make a difference in pain and is most effective when done in conjunction with exercise.

Regarding function, the effect of PNE was almost negligible but a very small effect was present in support of PNE, **Table 4**. Despite PNE not making any functional advancements to CLBP patients, it conversely did not increase the present functional limitations. It should also be noted that the assessment of function via validated outcome measures is graded as an "F" in the current clinical practice guidelines for low back pain, endorsed by the American Physical Therapy Association.[27] The reasoning for the low rating is that outcome measures are too heavily relied upon by practitioners and often cause the examination of individual function abilities to be deferred to global and subjective assessment.[27] Additionally, subjective reporting of function is emotionally liable and highly influenced by daily fluctuations.[27] Put simply, scores of subjective functional outcome measures do not reflect the true abilities of the individual and more objective measures could better present improvements without emotional influences. This is an especially imperative point, now that there is a heightened understanding of the emotional link, individuality, and complexity of pain that contribute to overall psychological well-being of a patient and moreover may explain why PNE demonstrated a reduction in pain but not functional gains.

The portions of the brain responsible for memory and behavioral output are also responsible for pain production. [7,17-19,35-37] It is of particular emphasis that behavior, emotion, memory, and pain are all created by the mesolimbic-prefrontal brain regions.[7,17-19,35-37] The mesolimbic-prefrontal areas influence motor production and descending modulating pathways from the brain; meaning certain behaviors or psychosocial dysfunctions can affect the way the body moves in response to pain or anticipated pain and whether painful signals receive inhibition contributing to abnormal responses and duration of pain.[17-19,35] Specific correlation is further demonstrated by chronic pain patients who typically produce the emotionally laden behavioral responses: fear-avoidance behaviors, post-traumatic stress syndrome, pain catastrophizing, and low self-efficacy.[7,17-19,35-37] The intertwining of these brain networks are further strengthened via the limbic system, the sensorimotor system, and the brainstem which all have direct and indirect connections to the somatosensory system and psychological pathways, explaining why a stimulus, emotion, or behavior produced in 1 system can cause effects to the other.[35] These links confirm that all pain, but especially chronic pain, is impacted by perceptions, memories, emotions, and stimuli in both the brain and the periphery.[7,17,18,37,66] Therefore, malfunctions in either the periphery or cortical regions, can cause maladaptive neuroplastic changes to the other, which illuminates a pivotal concept to understand and guide treatment for CLBP.

When an injury occurs, a natural response system is engaged to protect the body and initiate healing.[13,17,18,30-32,35,53,66-68] Part of the response is to make the tissues more sensitive to potential danger to prevent further damage until the injury is resolved; thus a previously harmless or less intense stimulus from the tissues would alert the brain of danger and increase the likelihood of pain as a response.[13,17,18,30-32,35,53,66-68] This process of amplified sensitivity in the body and

extremities is known as peripheral sensitization. [13,17,18,30-32,35,53,66-68] In consequence, the more frequent conduction of danger signals causes the brain to adapt by reducing the number of signals needed to produce pain for protection, creating a state of central sensitization. [13,17,18,30-32,35,53,66-68] The brain will further adjust by enlarging the painful body part in the primary sensory cortex to increase danger signal detection and cause blurring of the painful part in the primary motor cortex to reduce use. [13,17,18,30-32,35,53,66-68] Research shows that the changes that have occurred in the primary motor cortex will not improve with simple repetitive movements, but require focused attention, feedback, motivation, and varying task complexity all of which are initial components of motor learning and actions generated in the mesolimbic-prefrontal cortex of the brain.[17,18,31,32] Therefore, PNE can help reduce emotional complications and behavioral output through education of the pain cycle which could to demonstrate an immediate reduction in pain, but it cannot fully improve the function of a patient without exercise specifically directed at resolving the distorted body part of the motor homunculus. [17,18,31,32] Recent evidence also demonstrates that bottom-up interventions are not sufficient enough to correct the neuroplasticity of chronic pain in cortical regions, which means that central sensitization cannot be resolved through treatment of peripheral impairments alone.[13,17,18,31,32,53,69] Current physical therapy interventions use a bottom-up approach directing treatment at complications of peripheral sensitization: reduced strength, diminished proprioception, and impaired sensation.[17,18] These are the fundamental treatment interventions of the current clinical practice guidelines for CLBP.[3,26-29]

No current physical therapy intervention defined by clinical practice guidelines target central sensitization or highlight the importance of how multiple influencing components of life are connected to the pain centers of the brain.

Additionally, it has been recognized that using a biopsychosocial method of education, such as PNE, helps counteract not only the psychosocial, but biological and sociological influences on chronic pain.[11,30-32,53] Importantly, the currently used biomedical approach of education and treatment has demonstrated negative effects on emotional states connected with chronic pain[20,31,54,55] and isn't proving successful at reducing the incidence of CLBP based on the current epidemic. [2,3] PNE is a necessary educational component to a top-down approach to treating central sensitization changes of chronic pain; directed at effecting fear avoidance behaviors, pain catastrophizing, post-traumatic stress syndrome, decreased perceived social support, and low self-efficacy that contribute to the maladaptive prolonged pain response leading to neuroplastic alterations in both the brain and spinal cord.[9,11,14,17-24,30-32,69] There are additional top-down approaches of treatment that can be utilized after PNE is established as a baseline understanding: meditation, graded activity exposure, cognitive behavioral therapy addressing negative thoughts, mindfulness, and supervised exercise.[17,30-32,66,70,71] This evidence presents that the persistence of pain beyond the need for protection is perhaps sustained because of an overlooked psychosocial comorbidity affecting the mesolimbic-prefrontal neural connections of behavior and memories to pain, as well as the lack of physical therapy interventions that promote motor learning.[13,17,18,30-32,35,53,66-68] It is apparent that the complexities of chronic pain must all be addressed to help resolve CLBP and are not being accounted for in current physical therapy practices.

Limitations

This meta-analysis combines data across a small amount of studies in order to estimate treatment effects with more power than is possible in 1 study. The

main limitations of this meta-analysis are the articles available for evaluation. The current research is varied in the outcome measures used for both pain and function, the duration and frequency of the intervention, the number of subjects, the research designs allowing for validity threats and several research biases all of which make it difficult compile a large statistical power conclusion, explicitly in favor of PNE. In this analysis, the poor amount of power ultimately led to no effect due to the grand effect lines crossing the null effect line when examining the forest plots of the data. The flaws of the articles will be discussed further which can provide insight to explanations or abnormalities of the data and forest plots.

The outcome measures used in all of the studies rely upon subjective patient reporting, making this analysis susceptible to reliability and validity threats to the retesting of data and reproducibility of the results.[72] The populations selected for the studies increase the possibility of external validity threats: sampling bias based on subject recruitment through flyers posted at physical therapy clinics, other healthcare clinics, and a newspaper advertisement which limits the representation of CLBP from the global population and a voluntary bias due to the self-volunteered subjects who could be more ambitious or compliant towards health changes than the random CLBP patient.[64,73] Furthermore, internal validity threats can be found in the fact that none of the researchers were blinded to the administered treatment and inopportunely, Moseley et al.[45] has a financial interest in advancing the use of PNE making the research vulnerable to expectancy and performance biases.[64,73] Besides apparent restrictions in the generalization of the results of this analysis and limit of the research designs, the studies had other flaws that could contribute to malfunctions in the data. Two of the 3 articles did not present or publish data in complete or ordinary manner resulting in a reporting and publication biases.[64,73,74] Moseley et al.[45] never published the yielded pain

data, therefore it was necessary to obtain this information from another article, Clarke et al.,[41] in which the data were shared between the authors. Walti et al.[49] did not report standard deviations for data, thus it was calculated for this analysis making the information subject to error and decreased precision.

Internal validity threats are continued in the analyzed variables of this paper and in the individual articles, as well as help determine flaws in this study. Walti et al.[49] used several independent variables along with PNE convoluting the determination of which variable created change and produced a confounding variable bias.[64,73] In addition, each of the articles selected for this paper had similar but different outcome measures, which contribute to statistical error from discrepancies in the measurement scales despite correlation between the measures. Specifically, the VAPS and the NRS have shown excellent correlation[63] but, new evidence states that the 2 measures may not be interchangeable as it is not realistic that patients would provide equal levels of pain when presented with each of the scales.[75] This incompatibility would account for the effect size of the pain data point for Walti et al.[49] to be different than the other 2 articles, as the NRS was only used for this paper, and would ultimately decrease the total effect size. In addition the functional outcome measurements, the RMDQ and the QBPDS demonstrate moderate to large correlation at evaluating the same self-reported dysfunction.[60,62] However, the scales of measurement vary in the number of proposed tasks in the questionnaires: 24 items in the RMDQ and 20 items in the QBPDS, making the data mathematically inequivalent.[60,62] This would explain why the effect size for Pires et al.[47] was drastically different than the other 2 articles, as the QBPDS was only used in this article, causing the total effect size to be skewed and confounded data.

Aside from the use of mismatched outcome measures in this analysis, the duration and frequency of the intervention varies in each article making the reliability of the studies very difficult and limits the power of clinical effectiveness.[72] This analysis did demonstrate that PNE can have a small effect on CLBP reduction in either 1[45] or in 12 sessions,[47] giving some insight to time needed to make PNE effective and allowing for future research guidelines. It should be noted that the single session of PNE, given by Moseley et al.,[45] was provided for 3-hours and thus unfeasible for the average physical therapy treatment. Additionally, intervention subjects in both Pires et al.[47] and Walti et al.,[49] were given extra sessions or time periods in order to administer the PNE and the control groups were not compensated with additional time for biomedical education. The discrepancy in treatment time to the intervention group is another internal validity threat and can could be the root cause of any improvements.[47,74] Lastly, none of the studies have shown the effects of PNE on CLBP improvement lasting greater than three months making the current results insignificant at providing long-term changes.[45,47,49]

Conclusion

The intent of this paper was to demonstrate the psychosocial connection to pain that is missing in CLBP treatments. This link could reduce the growing CLBP incidence and help prevent acute injuries from progressing to chronic states. PNE is not meant to replace all physical therapy interventions, rather it should be used as a supplement to improve treatment sessions. This would be especially demonstrated in patient communication through the understanding of biological science of pain and injury, as well as the connection of emotions, beliefs, and memories to pain. The current biomedical education is not working, which is

clearly reflected in the CLBP epidemic. PNE has shown to diminish psychosocial factors during medical visits[20,31,54,55] and has a small effect on reducing CLBP, making it a logical substitution to the current biomedical education. Additional studies need to be performed with continued analysis of PNE with physical therapy interventions defined by clinical practice guidelines and current physical therapy interventions alone. Studies should also examine minimal dosing required to make short and long-term changes for CLBP reduction and evaluation of improvement of non-subjective measurements of function.

REFERENCES

REFERENCES

1. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine.* 2008;8(1):8-20. doi:10.1016/j.spinee.2007.10.005.

2. Gore M, Sadosky A, Stacey BR, Tai KS, Leslie D. The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. *Spine.* 2012;37(11):E668-677. doi:10.1097/BRS.0b013e318241e5de.

3. Herndon CM, Zoberi KS, Gardner BJ. Common questions about chronic low back pain. *Am Fam Physician.* 2015;91(10):708-714.

4. Hoy D, Brooks P, Blyth F, Buchbinder R. The Epidemiology of low back pain. *Best Prac Res Clin Rheumatol.* 2010;24(6):769-781. doi:10.1016/j.berh.2010.10.002.

5. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine.* 2008;8(1):8-20. doi:10.1016/j.spinee.2007.10.005.

6. Gore M, Sadosky A, Stacey BR, Tai KS, Leslie D. The burden of chronic low back pain: clinical comorbidities, treatment patterns, and health care costs in usual care settings. *Spine.* 2012;37(11):E668-677. doi:10.1097/BRS.0b013e318241e5de.

7. Herndon CM, Zoberi KS, Gardner BJ. Common questions about chronic low back pain. *Am Fam Physician.* 2015;91(10):708-714.

8. Hoy D, Brooks P, Blyth F, Buchbinder R. The Epidemiology of low back pain. *Best Prac Res Clin Rheumatol.* 2010;24(6):769-781. doi:10.1016/j.berh.2010.10.002.

9. Hoy D, Bain C, Williams G, et al. A systematic review of the global prevalence of low back pain. *Arthritis Rheum.* 2012;64(6):2028-2037. doi:10.1002/art.34347.

10. Mehra M, Hill K, Nicholl D, Schadrack J. The burden of chronic low back pain with and without a neuropathic component: a healthcare resource use and cost analysis. *J Med Econ.* 2012;15(2):245-252. doi:10.3111/13696998.2011.642090.

11. Gallagher RM. Biopsychosocial pain medicine and mind-brain-body science. *Phys Med Rehabil Clin N Am.* 2004;15(4):855-882.

12. Nicholas MK, Linton SJ, Watson PJ, Main CJ. Early identification and management of psychological risk factors ("yellow flags") in patients with low back pain: a reappraisal. *Phys Ther.* 2011;91(5):737-753. doi:10.2522/ptj.20100224.

13. Nijs J, Goubert D, Ickmans K. Recognition and Treatment of Central Sensitization in Chronic Pain Patients: Not Limited to Specialized Care. *J Orthop Sports Phys Ther.* 2016;46(12):1024-1028. doi:10.2519/jospt.2016.0612.

14. Hill JC, Fritz JM. Psychosocial influences on low back pain, disability, and response to treatment. *Phys Ther.* 2011;91(5):712-721. doi:10.2522/ptj.20100280.

15. Hasenbring MI, Pincus T. Effective reassurance in primary care of low back pain: what messages from clinicians are most beneficial at early stages? *Clin J Pain.* 2015;31(2):133-136. doi:10.1097/ajp.0000000000000097.

16. Main CJ, George SZ. Psychologically Informed Practice for Management of Low Back Pain: Future Directions in Practice and Research. *Phys Ther.* 2011;91(5):820-824. doi:10.2522/ptj.20110060.

17. Pelletier R, Higgins J, Bourbonnais D. Addressing Neuroplastic Changes in Distributed Areas of the Nervous System Associated With Chronic Musculoskeletal Disorders. *Phys Ther.* 2015;95(11):1582-1591. doi:10.2522/ptj.20140575.

18. Pelletier R, Higgins J, Bourbonnais D. Is neuroplasticity in the central nervous system the missing link to our understanding of chronic musculoskeletal disorders? *BMC Musculoskelet Disord.* 2015;16:25. doi:10.1186/s12891-015-0480-y.

19. Simons LE, Elman I, Borsook D. Psychological processing in chronic pain: a neural systems approach. *Neurosci Biobehav Rev.* 2014;39:61-78. doi:10.1016/j.neubiorev.2013.12.006.

20. Darlow B, Dowell A, Baxter GD, Mathieson F, Perry M, Dean S. The enduring impact of what clinicians say to people with low back pain. *Ann Fam Med.* 2013;11(6):527-534. doi:10.1370/afm.1518.

21. Meyer K, Tschopp A, Sprott H, Mannion AF. Association between catastrophizing and self-rated pain and disability in patients with chronic low back pain. *J Rehabil Med.* 2009;41(8):620-625. doi:10.2340/16501977-0395.

22. Rainville J, Smeets RJ, Bendix T, Tveito TH, Poiraudeau S, Indahl AJ. Fear-avoidance beliefs and pain avoidance in low back pain--translating research into clinical practice. *Spine.* 2011;11(9):895-903. doi:10.1016/j.spinee.2011.08.006.

23. Wertli MM, Eugster R, Held U, Steurer J, Kofmehl R, Weiser S. Catastrophizing-a prognostic factor for outcome in patients with low back pain: a systematic review. *Spine.* 2014;14(11):2639-2657. doi:10.1016/j.spinee.2014.03.003.

24. Wertli MM, Rasmussen-Barr E, Held U, Weiser S, Bachmann LM, Brunner F. Fear-avoidance beliefs-a moderator of treatment efficacy in patients with low back pain: a systematic review. *Spine.* 2014;14(11):2658-2678. doi:10.1016/j.spinee.2014.02.033.

25. Foster NE, Delitto A. Embedding Psychosocial Perspectives Within Clinical Management of Low Back Pain: Integration of Psychosocially Informed Management Principles Into Physical Therapist Practice--Challenges and Opportunities. *Phys Ther.* 2011;91(5):790-803. doi:10.2522/ptj.20100326.

26. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Int Med.* 2017;166(7):493-505. doi:10.7326/M16-2459.

27. Delitto A GS, Van Dillen L, Whitman J, Sowa G, Shekelle P, Denninger T, Godges J. Low Back Pain: Clinical Practice Guidelines Linked to the ICF, Disability, and Health from the Orthopedic Section of the APTA. *J Orthop Sports Phys Ther.* 2012;42(4):A1-A57.

28. Koes BW, van Tulder M, Lin CW, Macedo LG, McAuley J, Maher C. An updated overview of clinical guidelines for the management of non-specific low back pain in primary care. *Eur Spine J.* 2010;19(12):2075-2094. doi:10.1007/s00586-010-1502-y.

29. Qaseem A, Wilt TJ, McLean RM, Forciea MA. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline From the American College of Physicians. *Ann Int Med.* 2017;166(7):514-530. doi:10.7326/M16-2367.

30. Louw A. *Why Do I Hurt? A Patient Book About the Neuroscience of Pain.* Vol 1. Minneapolis, MN: Orthopedic Physical Therapy Products; 2013.

31. Butler D ML. *Explain Pain.* 2 ed. Adelaide, Australia: Neuro Orthopedic Institute Group; 2013.

32. Moseley GL, Butler, D.S. *Explain Pain Supercharged.* 1st ed. South Australia: Noigroup Publications; 2017.

33. Louw A, Zimney K, O'Hotto C, Hilton S. The clinical application of teaching people about pain. *Physiother Theory Prac.* 2016;32(5):385-395. doi:10.1080/09593985.2016.1194652.

34. Moseley GL. Reconceptualising pain according to modern pain science. *Phys Ther.* 2007;12(3):169-178.

35. Dickenson A. The neurobiology of chronic pain states. *An Intensive Care Med.* 2013;14(11):484-487. doi:https://doi.org/10.1016/j.mpaic.2013.08.008.

36. Melzack R, Katz J. Pain. *Wiley interdisciplinary reviews Cognitive science.* 2013;4(1):1-15. doi:10.1002/wcs.1201.

37. Moseley GL. A pain neuromatrix approach to patients with chronic pain. *Man Ther.* 2003;8(3):130-140.

38. Moseley GL, Butler DS. Fifteen Years of Explaining Pain: The Past, Present, and Future. *J Pain.* 2015;16(9):807-813. doi:10.1016/j.jpain.2015.05.005.

39. Louw A, Diener I, Butler DS, Puentedura EJ. The Effect of Neuroscience Education on Pain, Disability, Anxiety, and Stress in Chronic Musculoskeletal Pain. *Arch Phys Med Rehabil.* 2011;92(12):2041-2056. doi:10.1016/j.apmr.2011.07.198.

40. Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience education on musculoskeletal pain: A systematic review of the literature. *Physiothe Theory Prac.* 2016;32(5):332-355. doi:10.1080/09593985.2016.1194646.

41. Clarke CL, Ryan CG, Martin DJ. Pain neurophysiology education for the management of individuals with chronic low back pain: systematic review and meta-analysis. *Man Ther.* 2011;16(6):544-549. doi:10.1016/j.math.2011.05.003.

42. Louw A, Diener I, Landers MR, Puentedura EJ. Preoperative pain neuroscience education for lumbar radiculopathy: a multicenter randomized controlled trial with 1-year follow-up. *Spine.* 2014;39(18):1449-1457. doi:10.1097/brs.0000000000000444.

43. Louw A, Nijs J, Puentedura EJ. A clinical perspective on a pain neuroscience education approach to manual therapy. *J Man Manip Ther.* 2017;25(3):160-168. doi:10.1080/10669817.2017.1323699.

44. Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. *Eur J Pain.* 2004;8(1):39-45. doi:10.1016/s1090-3801(03)00063-6.

45. Moseley GL, Nicholas MK, Hodges PW. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clin J Pain.* 2004;20(5):324-330.

46. Moseley L. Combined physiotherapy and education is efficacious for chronic low back pain. *Aust J Physiother.* 2002;48(4):297-302.

47. Pires D, Cruz EB, Caeiro C. Aquatic exercise and pain neurophysiology education versus aquatic exercise alone for patients with chronic low back pain: a randomized controlled trial. *Clin Rehabil.* 2015;29(6):538-547. doi:10.1177/0269215514549033.

48. Van Oosterwijck J, Nijs J, Meeus M, et al. Pain neurophysiology education improves cognitions, pain thresholds, and movement performance in people with chronic whiplash: A pilot study. *J Rehabil Res Devel.* 2011;48(1):43-57. doi:10.1682/JRRD.2009.12.0206.

49. Wälti P, Kool J, Luomajoki H. Short-term effect on pain and function of neurophysiological education and sensorimotor retraining compared to usual physiotherapy in patients with chronic or recurrent non-specific low back pain, a pilot randomized controlled trial. *BMC Musculoskelet Disord.* 2015;16(1):83-83. doi:10.1186/s12891-015-0533-2.

50. Moseley L. Unraveling the barriers to reconceptualization of the problem in chronic pain: the actual and perceived ability of patients and health professionals to understand the neurophysiology. *J Pain.* 2003;4(4):184-189.

51. Tellez-Garcia M, de-la-Llave-Rincon AI, Salom-Moreno J, Palacios-Cena M, Ortega-Santiago R, Fernandez-de-Las-Penas C. Neuroscience education in addition to trigger point dry needling for the management of patients with mechanical chronic low back pain: A preliminary clinical trial. *J Bodyw Mov Ther.* 2015;19(3):464-472. doi:10.1016/j.jbmt.2014.11.012.

52. Ryan CG, Gray HG, Newton M, Granat MH. Pain biology education and exercise classes compared to pain biology education alone for individuals with chronic low back pain: a pilot randomised controlled trial. *Man Ther.* 2010;15(4):382-387. doi:10.1016/j.math.2010.03.003.

53. Nijs J, Roussel N, Paul van Wilgen C, Koke A, Smeets R. Thinking beyond muscles and joints: therapists' and patients' attitudes and beliefs regarding chronic musculoskeletal pain are key to applying effective treatment. *Man Ther.* 2013;18(2):96-102. doi:10.1016/j.math.2012.11.001.

54. Morr S, Shanti N, Carrer A, Kubeck J, Gerling MC. Quality of information concerning cervical disc herniation on the Internet. *Spine.* 2010;10(4):350-354. doi:10.1016/j.spinee.2010.02.009.

55. Louw A, Zimney K, Johnson E, Kraemer C, Fesler J, Burcham T. De-educate to re-educate: aging and low back pain. *Aging Clin Exp Res.* 2017;29(6):1261-1269. doi:10.1007/s40520-017-0731-x.

56. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg.* 2011;128(1):305-310. doi:10.1097/PRS.0b013e318219c171.

57. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. *Aust J Physiother.* 2009;55(2):129-133.

58. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro Scale for rating quality of randomized controlled trials. *Phys Ther.* 2003;83(8):713-721.

59. Harland NJ, Dawkin MJ, Martin D. Relative utility of a visual analogue scale vs a six-point Likert scale in the measurement of global subject outcome in patients with low back pain receiving physiotherapy. *Physiotherapy.* 2015;101(1):50-54. doi:10.1016/j.physio.2014.06.004.

60. The Roland Morris Disability Questionnaire. *J Physiother.* 2016;62(2):116-116.

61. Stratford PW, Riddle DL. A Roland Morris Disability Questionnaire Target Value to Distinguish between Functional and Dysfunctional States in People with Low Back Pain. *Physiother Can.* 2016;68(1):29-35. doi:10.3138/ptc.2014-85.

62. Quebec Back Pain Disability Scale. 2013; https://www.physio-pedia.com/Quebec_Back_Pain_Disability_Scale#cite_note-calmels-4. Accessed January 10th, 2015, 2013.

63. Shirley Ryan Ability Lab. Numeric Pain Rating Scale. 2004; https://www.sralab.org/rehabilitation-measures/numeric-pain-rating-scale. Accessed January, 10, 2017.

64. Portney LG WM. *Foundations of Clinical Research: Application to Practice.* 3rd ed. New Jersey: Pearson Education 2009.

65. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ Clin Res.* 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557.

66. Campbell CM, Edwards RR, Campbell CM, Edwards RR. Mind-body interactions in pain: the neurophysiology of anxious and catastrophic pain-related thoughts. *J Lab Clin Med.* 2009;153(3):97-101. doi:10.1016/j.trsl.2008.12.002.

67. Nijs J, Meeus M, Cagnie B, et al. A Modern Neuroscience Approach to Chronic Spinal Pain: Combining Pain Neuroscience Education With Cognition-Targeted Motor Control Training. *Phys Ther.* 2014;94(5):730-738. doi:10.2522/ptj.20130258.

68. Nijs J, Paul van Wilgen C, Van Oosterwijck J, van Ittersum M, Meeus M. How to explain central sensitization to patients with 'unexplained' chronic musculoskeletal pain: practice guidelines. *Man Ther.* 2011;16(5):413-418. doi:10.1016/j.math.2011.04.005.

69. Roy JS, Bouyer LJ, Langevin P, Mercier C. Beyond the Joint: The Role of Central Nervous System Reorganizations in Chronic Musculoskeletal Disorders. *J Orthop Sports Phys Ther.* 2017;47(11):817-821. doi:10.2519/jospt.2017.0608.

70. Nicholas MK, George SZ. Psychologically Informed Interventions for Low Back Pain: An Update for Physical Therapists. *Phys Ther.* 2011;91(5):765-776. doi:10.2522/ptj.20100278.

71. Narasimhan M, Campbell N. A tale of two comorbidities: understanding the neurobiology of depression and pain. *Indian J Psych.* 2010;52(2):127-130. doi:10.4103/0019-5545.64586.

72. Elasy TA, Gaddy G. Measuring subjective outcomes: rethinking reliability and validity. *J Gen Intern Med.* 1998;13(11):757-761.

73. Malone H, Nicholl H, Tracey C. Awareness and minimisation of systematic bias in research. *Br J Nurs.* 2014;23(5):279-282.

74. Theodore BR, Gatchel RJ. Management and interpretation of data obtained from clinical trials in pain management. *Pain Prac.* 2008;8(6):461-472.

75. Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symp Manage.* 2011;41(6):1073-1093. doi:10.1016/j.jpainsymman.2010.08.016.

TABLES

Table 1. PEDro Quality Assessment

	Moseley et al. 2004	Pires et al. 2015	Walti et al/ 2015
1. Eligibility Criteria	Yes	Yes	Yes
2. Random Allocation	Yes	Yes	Yes
3. Allocation Concealment	Yes	Yes	Yes
4. Similar at Baseline	Yes	Yes	Yes
5. Blinding of Subjects	No	No	No
6. Blinding of Therapists	No	No	No
7. Blinding of Assessors	No	Yes	Yes
8. Adequate Follow-up	Yes	Yes	Yes
9. Intent to Treat Analysis	No	Yes	Yes
10. Between Group Comparison	Yes	Yes	Yes
11. Point Estimate and Variability	Yes	Yes	Yes
Total Score	6/10	8/10	8/10
Quality	High	HIgh	High

Table 2. Individual Study Summaries

Study	Participants	Intervention (PNE)	Control	Duration	Outcome Measures	Results
Moseley et al. 2004	PNE: 31 Control: 27	-3 hours 1:1 PNE -Workbook for 15 days.	-3 hours 1:1 biomedical education - Workbook for 15 days.	-1 session education -15 days of homework -Assessment 15 days after baseline	VAS RMDQ SOPAR PCS SLR FBR ADIT	Significant improvement with PNE vs. control: for RMDQ, SPOAR, PCS, SLR, FBR
Pires et al. 2015	PNE: 30 Control: 32	-2 x week of aquatic exercise 30-50 mins -2 sessions of PNE 90 mins	-2 x week of aquatic exercise 30-50 mins each	-2 x a week for 6 weeks -Assessment 6 weeks after baseline -Assessment 3 months after baseline	VAS QBPDS TSK	Significant improvement with PNE vs. control for: VAS at 6 weeks, but not at 3 months
Walti et al. 2015	PNE: 14 Control: 13	-PT 1- 2 x week x 8 weeks with 16 max -HEP 30 mins 5 x week -PNE in 2-4 sessions Explain Pain book. -Sensory training -Motor training.	-PT 1- 2 x week x 8 weeks with 16 max -HEP 30 mins 5 x week -Basic education about exacerbation of pain	-Assessment 12 weeks after baseline	NRS PSFS RMDQ FABQ PCS TPD	Significant improvement with PNE vs. control: for NRS

PNE= Pain Neurophysiology Education, VAS= Visual Analogue Scale, RMDQ= Roland Morris Disability Questionnaire, SOPAR= Survey of Pain Attitudes Revised, PCS= Pain Catastrophizing Scale, SLR= Straight Leg Raise, FBR= Forward Bending Range, ADIT= Abdominal Drawing In Test, QBPDS= Quebec Back Pain Disability Scale, TSK= Tampa Scale of Kinesiophobia, NRS= Numeric Rating Scale, PSFS= Patient Specific Functional Scale, FABQ= Fear Avoidance Belief Questionnaire, TPD= Two-Point Discrimination

Table 3. Pain Effect Size and Homogeneity Analysis

Study	Effect Size	SE of Effect Size	CI Lower	CI Upper
Moseley et al. 2004	-0.27	0.26	-0.78	0.25
Pires et al. 2015	-0.39	0.26	-0.89	0.12
Walti et al. 2015	0.32	0.39	-0.44	1.08
			Total Effect Size	-0.21
			Combined CI Upper	0.12
			Combined CI Lower	-0.53
			I^2	15.97%
			Q-Value	2.381033481
			P-value	0.304064101

Table 4. Function Effect Size and Homogeneity Analysis

Study	Effect Size	SE of Effect Size	CI Lower	CI Upper
Moseley et al. 2004	-0.67	0.27	-1.20	-0.14
Pires et al. 2015	0.06	0.25	-0.44	0.55
Walti et al. 2015	0.78	0.40	0.00	1.57
			Total Effect Size	-0.09
			Combined CI Upper	0.24
			Combined CI Lower	-0.42
			I^2	100%
			Q-Value	9.659099035
			P-Value	0.00799012

FIGURES

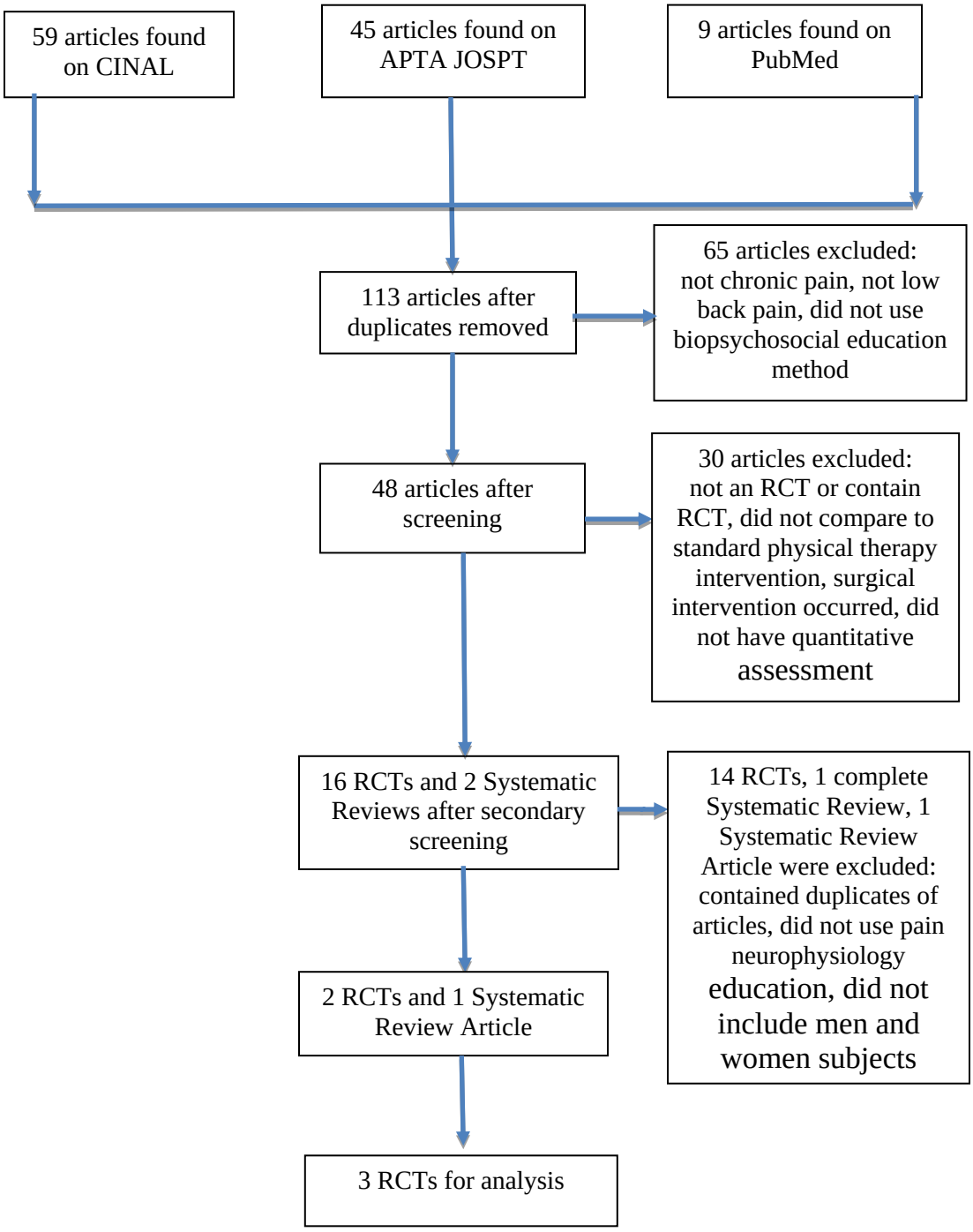

Figure 1. Consort

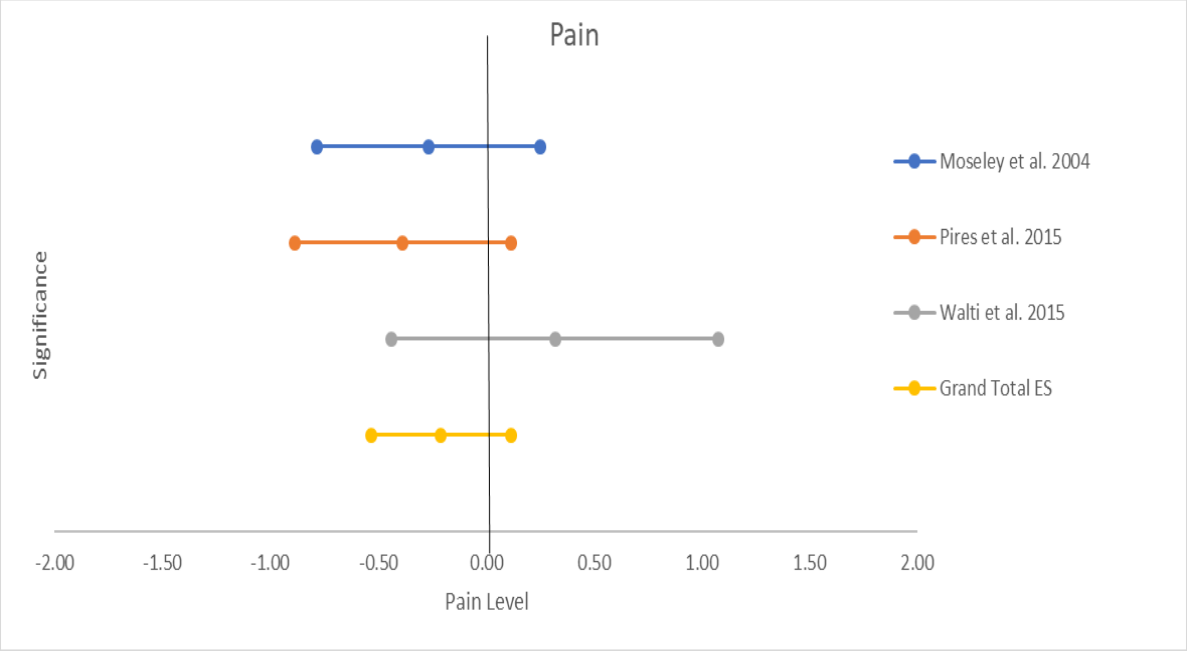

Figure 2. Forest plot for effect size of pain

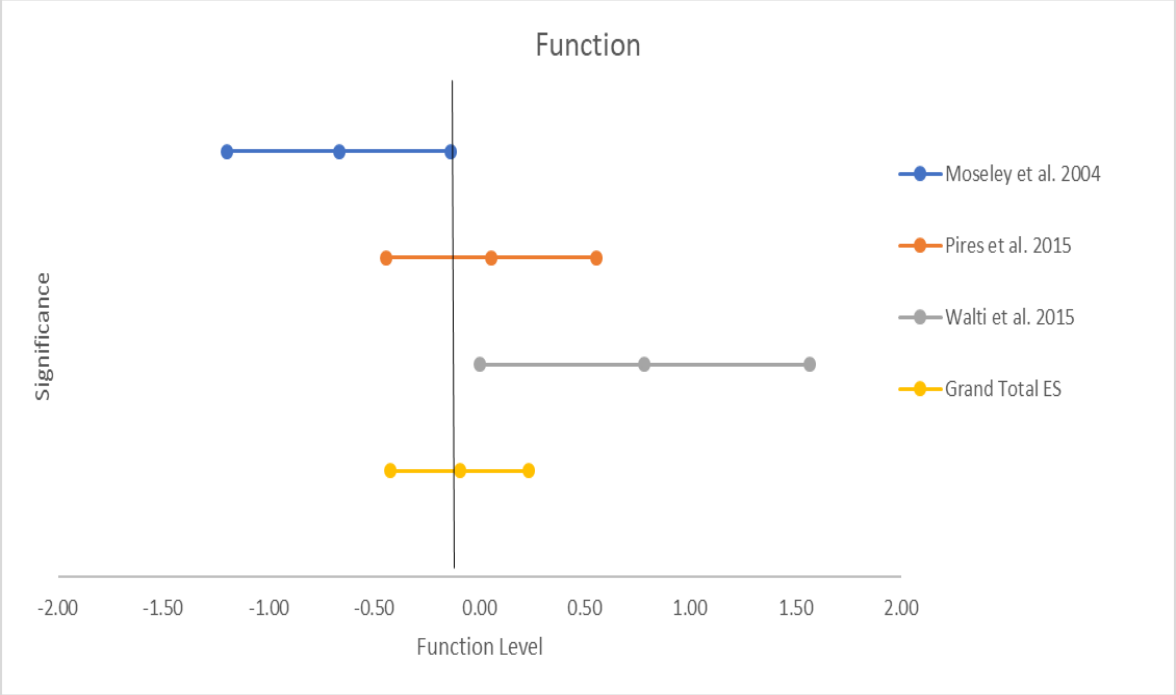

Figure 3. Forest plot for effect size of function

APPENDIX: PEDRO SCALE

PEDro scale

1.	eligibility criteria were specified	no ❑ yes ❑ where:
2.	subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received)	no ❑ yes ❑ where:
3.	allocation was concealed	no ❑ yes ❑ where:
4.	the groups were similar at baseline regarding the most important prognostic indicators	no ❑ yes ❑ where:
5.	there was blinding of all subjects	no ❑ yes ❑ where:
6.	there was blinding of all therapists who administered the therapy	no ❑ yes ❑ where:
7.	there was blinding of all assessors who measured at least one key outcome	no ❑ yes ❑ where:
8.	measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups	no ❑ yes ❑ where:
9.	all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"	no ❑ yes ❑ where:
10.	the results of between-group statistical comparisons are reported for at least one key outcome	no ❑ yes ❑ where:
11.	the study provides both point measures and measures of variability for at least one key outcome	no ❑ yes ❑ where:

The PEDro scale is based on the Delphi list developed by Verhagen and colleagues at the Department of Epidemiology, University of Maastricht (*Verhagen AP et al (1998). The Delphi list: a criteria list for quality assessment of randomised clinical trials for conducting systematic reviews developed by Delphi consensus. Journal of Clinical Epidemiology, 51(12):1235-41*). The list is based on "expert consensus" not, for the most part, on empirical data. Two additional items not on the Delphi list (PEDro scale items 8 and 10) have been included in the PEDro scale. As more empirical data comes to hand it may become possible to "weight" scale items so that the PEDro score reflects the importance of individual scale items.

The purpose of the PEDro scale is to help the users of the PEDro database rapidly identify which of the known or suspected randomised clinical trials (ie RCTs or CCTs) archived on the PEDro database are likely to be internally valid (criteria 2-9), and could have sufficient statistical information to make their results interpretable (criteria 10-11). An additional criterion (criterion 1) that relates to the external validity (or "generalisability" or "applicability" of the trial) has been retained so that the Delphi list is complete, but this criterion will not be used to calculate the PEDro score reported on the PEDro web site.

The PEDro scale should not be used as a measure of the "validity" of a study's conclusions. In particular, we caution users of the PEDro scale that studies which show significant treatment effects and which score highly on the PEDro scale do not necessarily provide evidence that the treatment is clinically useful. Additional considerations include whether the treatment effect was big enough to be clinically worthwhile, whether the positive effects of the treatment outweigh its negative effects, and the cost-effectiveness of the treatment. The scale should not be used to compare the "quality" of trials performed in different areas of therapy, primarily because it is not possible to satisfy all scale items in some areas of physiotherapy practice.

Last amended June 21st, 1999

Notes on administration of the PEDro scale:

All criteria	**Points are only awarded when a criterion is clearly satisfied**. If on a literal reading of the trial report it is possible that a criterion was not satisfied, a point should not be awarded for that criterion.
Criterion 1	This criterion is satisfied if the report describes the source of subjects and a list of criteria used to determine who was eligible to participate in the study.
Criterion 2	A study is considered to have used random allocation if the report states that allocation was random. The precise method of randomisation need not be specified. Procedures such as coin-tossing and dice-rolling should be considered random. Quasi-randomisation allocation procedures such as allocation by hospital record number or birth date, or alternation, do not satisfy this criterion.
Criterion 3	*Concealed allocation* means that the person who determined if a subject was eligible for inclusion in the trial was unaware, when this decision was made, of which group the subject would be allocated to. A point is awarded for this criteria, even if it is not stated that allocation was concealed, when the report states that allocation was by sealed opaque envelopes or that allocation involved contacting the holder of the allocation schedule who was "off-site".
Criterion 4	At a minimum, in studies of therapeutic interventions, the report must describe at least one measure of the severity of the condition being treated and at least one (different) key outcome measure at baseline. The rater must be satisfied that the groups' outcomes would not be expected to differ, on the basis of baseline differences in prognostic variables alone, by a clinically significant amount. This criterion is satisfied even if only baseline data of study completers are presented.
Criteria 4, 7-11	*Key outcomes* are those outcomes which provide the primary measure of the effectiveness (or lack of effectiveness) of the therapy. In most studies, more than one variable is used as an outcome measure.
Criterion 5-7	*Blinding* means the person in question (subject, therapist or assessor) did not know which group the subject had been allocated to. In addition, subjects and therapists are only considered to be "blind" if it could be expected that they would have been unable to distinguish between the treatments applied to different groups. In trials in which key outcomes are self-reported (eg, visual analogue scale, pain diary), the assessor is considered to be blind if the subject was blind.
Criterion 8	This criterion is only satisfied if the report explicitly states *both* the number of subjects initially allocated to groups *and* the number of subjects from whom key outcome measures were obtained. In trials in which outcomes are measured at several points in time, a key outcome must have been measured in more than 85% of subjects at one of those points in time.
Criterion 9	An *intention to treat* analysis means that, where subjects did not receive treatment (or the control condition) as allocated, and where measures of outcomes were available, the analysis was performed as if subjects received the treatment (or control condition) they were allocated to. This criterion is satisfied, even if there is no mention of analysis by intention to treat, if the report explicitly states that all subjects received treatment or control conditions as allocated.
Criterion 10	A *between-group* statistical comparison involves statistical comparison of one group with another. Depending on the design of the study, this may involve comparison of two or more treatments, or comparison of treatment with a control condition. The analysis may be a simple comparison of outcomes measured after the treatment was administered, or a comparison of the change in one group with the change in another (when a factorial analysis of variance has been used to analyse the data, the latter is often reported as a group × time interaction). The comparison may be in the form hypothesis testing (which provides a "p" value, describing the probability that the groups differed only by chance) or in the form of an estimate (for example, the mean or median difference, or a difference in proportions, or number needed to treat, or a relative risk or hazard ratio) and its confidence interval.
Criterion 11	A *point measure* is a measure of the size of the treatment effect. The treatment effect may be described as a difference in group outcomes, or as the outcome in (each of) all groups. *Measures of variability* include standard deviations, standard errors, confidence intervals, interquartile ranges (or other quantile ranges), and ranges. Point measures and/or measures of variability may be provided graphically (for example, SDs may be given as error bars in a Figure) as long as it is clear what is being graphed (for example, as long as it is clear whether error bars represent SDs or SEs). Where outcomes are categorical, this criterion is considered to have been met if the number of subjects in each category is given for each group.