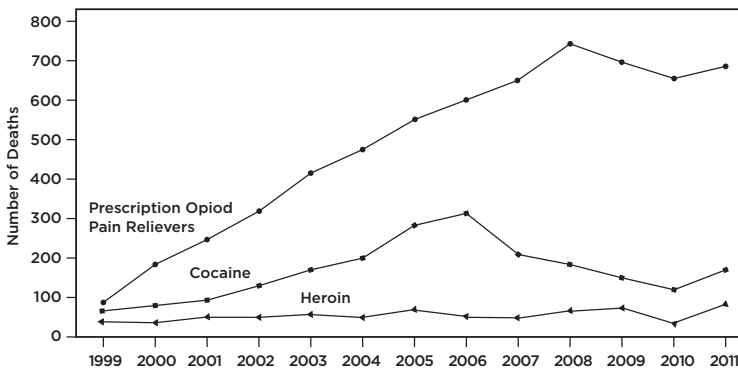


# Pain Neuroscience Education 101

## Pain Epidemic

It is currently reported that 25.3 million adults in the United States (US) are suffering from daily chronic pain.<sup>1,2</sup> Furthermore, it is estimated that 126.1 million adults in the US experience some pain over a 3 month reporting period.<sup>1,2</sup> Even children and adolescents struggle with persistent pain with various studies reporting approximately one in six experiencing persistent pain.<sup>3-5</sup> Within these staggering prevalence numbers is the associated cost of persistent pain in the US which adds an economic burden of \$560-635 billion dollars annually.<sup>1,2</sup> Beyond the financial costs lies the psychological and social consequences for the individual and those closely connected to that person. In 2012 US healthcare providers wrote 259 million prescriptions for opioid pain medications.<sup>6</sup> Americans, constituting only 5% of the world's population, have been consuming 80% of the global opioid supply, and 99% of the global hydrocodone supply<sup>7</sup> and the Centers for Disease Control (CDC) reports prescription opioids causing 3 times more annual fatalities than heroin and cocaine combined.<sup>8</sup> It is clear that something significant regarding pain must change in the US.

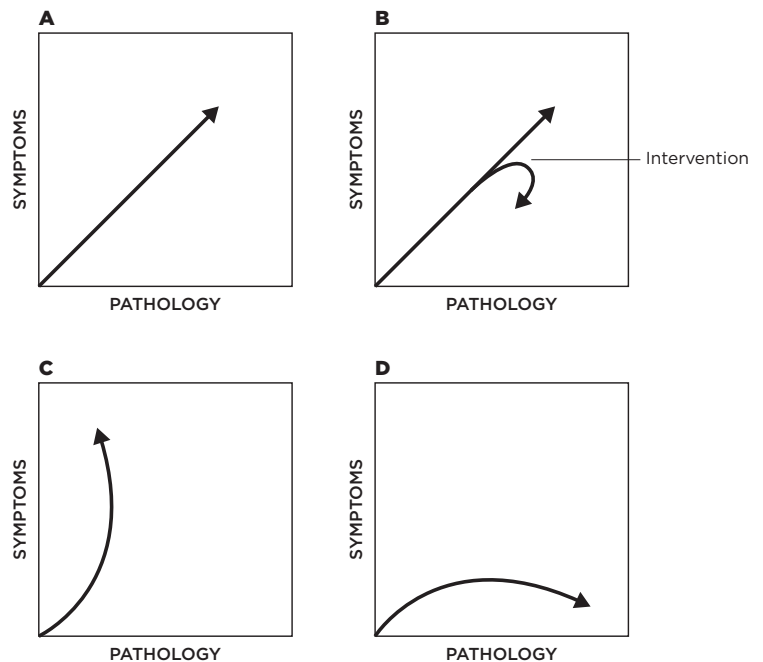


## Why this problem with pain?

Although the solution to the pain epidemic is most likely multi-factorial, one potential part of the solution may be changing how people view pain.<sup>9,10</sup> Pain is a normal human experience and essential for survival.<sup>10</sup> It can be argued that pain cannot and should not be prevented, but what a person does when they experience pain, may be far more important than the pain experienced itself.<sup>9,11</sup> Numerous studies have shown that coping skills and coping behaviors powerfully predict persistent pain and disability.<sup>12,13</sup> It is intriguing to consider that seemingly similar people may experience a similar injury, yet recover very differently in terms of duration, pain intensity, progression and healthcare utilization.<sup>14,15</sup> When it comes to pain, however, a fundamental part of coping with it relates to how much

a person knows about pain.<sup>16</sup> Traditional pain education models have connected the health of tissues to pain, yet it is well documented that the health of tissues and pain do not necessarily correlate.<sup>17-19</sup> As long as patients, healthcare providers and the general population connect the health of tissues to how much pain someone will experience, it can increase fear-avoidance and pain catastrophization, which have been shown to be powerful predictors of persistent pain, culminating in a viscous cycle.<sup>20,21</sup>

In line with the commonly held belief that tissue health and pain are correlated, traditional educational models teaching people about pain have similarly focused on anatomical, pathoanatomical and biomechanical explanations.<sup>22</sup> In acute, sub-acute or perioperative conditions, these biomedical explanations may be helpful to explain the pathology and biomechanics of the injury portion of a pain experience to patients, but they fall short of explaining persistent pain.<sup>10,22</sup> Additionally, there is growing evidence that biomedical models used in explaining a pain experience may actually induce more fear and anxiety, which in turn have been linked to the development and maintenance of persistent pain.<sup>23,24</sup> It is within these traditional models that a clinical and potentially, societal, dichotomy exists that adds to the current pain epidemic.<sup>9,25</sup> This dichotomy refers to the poor correlation between the health of a person's tissues and the pain they may be experiencing.<sup>10,17</sup> Most traditional pain models have perpetuated a model whereby the level of tissue injury and pain and disability were seen as synonymous, which is contrary to emerging pain science research.<sup>18,19</sup>



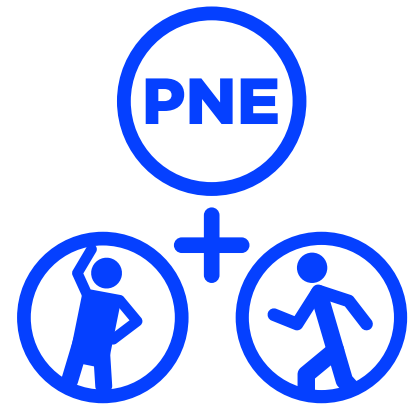
Some specific issues pertaining to Pain Neuroscience Education:



Delivered primarily by physical therapists as verbal one-on-one education with the use of metaphors, examples, pictures and books.<sup>28,33</sup>



Typically delivered in fifteen to thirty minute sessions once or twice a week for four to six weeks.<sup>34-37</sup>



PNE combined with movement and exercise is superior to education alone in decreasing pain and disability.<sup>28,33</sup>

Guide to Abbreviations:

**NNT:** The numbers needed to treat (NNT) refers to the effectiveness of a treatment. The lower the number, the more effective the treatment. For chronic pain the NNT refers to when patients experience a 50% reduction in pain or dysfunction. For example, the NNT for PNE shows that for every 3 people who receives PNE, one in three end up with a 50% reduction in pain. In comparison, when patients with chronic pain receive gabapentin, one in 6 end up with a pain reduction of 50% in a similar time frame.

**SSRI:** Selective Serotonin Reuptake Inhibitor. Examples include Celexa,<sup>TM</sup> Lexapro,<sup>TM</sup> Prozac,<sup>TM</sup> Paxil,<sup>TM</sup> and Zoloft.<sup>TM</sup>





**OLD APPROACH**

Patient has low back and leg pain.

**NEW APPROACH**



Patient consults with spine surgeon and decides to undergo low-back surgery. Surgeon gives patient 10-15 minutes of preoperative education regarding the surgery, procedures and recovery.



Patient also visits a physical therapist for preoperative education regarding pain science and a booklet to take home.

- 1 visit
- 30 minutes
- \$3 booklet



Patient undergoes low-back surgery.



**Patient is tracked for one year after surgery.**



Patient doesn't understand how pain works and worries about post-operative pain. Patient undergoes additional imaging, tests and treatments.

Patient understands what pain is and how it works and has realistic expectations for post-operative pain. Patient undergoes standard follow-up.



After one year, both patients have the same outcome regarding back pain, leg pain, fear of work, fear of physical activity, pain catastrophization and function. Substantial differences are observed in average cost and level of satisfaction.

Patient is significantly less satisfied with surgery.

Average cost for imaging, tests and treatments:

**\$4,833**

Average cost for imaging, tests and treatments:

45% savings **\$2,678**

Patient is significantly more satisfied with surgery.

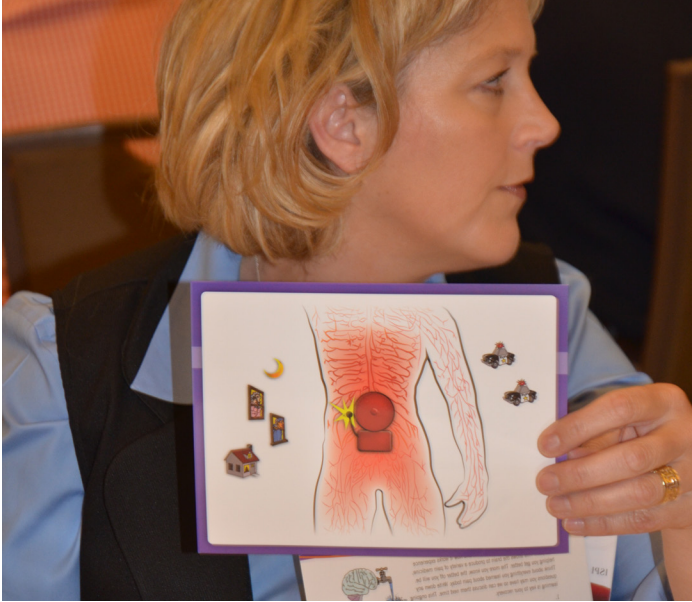
**600,000 discectomies** were performed in the US in 2012

If the cost savings per patient were applied, it would account for an annual savings of **\$1.2 billion**



## Pain Neuroscience Education

In recent years, born out of this dichotomy, clinicians and scientists explored the notion of teaching people more about pain.<sup>26,27</sup> This type of education is referred to as pain neuroscience education (PNE).<sup>11,28-30</sup> PNE is an educational strategy used by physical therapists that focuses on teaching people in pain more about the biological and physiological processes involved in their pain experience.<sup>27,31,32</sup> Current best-evidence provides strong support for PNE to positively influence pain ratings, dysfunctions, fear-avoidance, and pain catastrophization, limitations in movement, pain knowledge and healthcare utilization.<sup>28,33</sup>

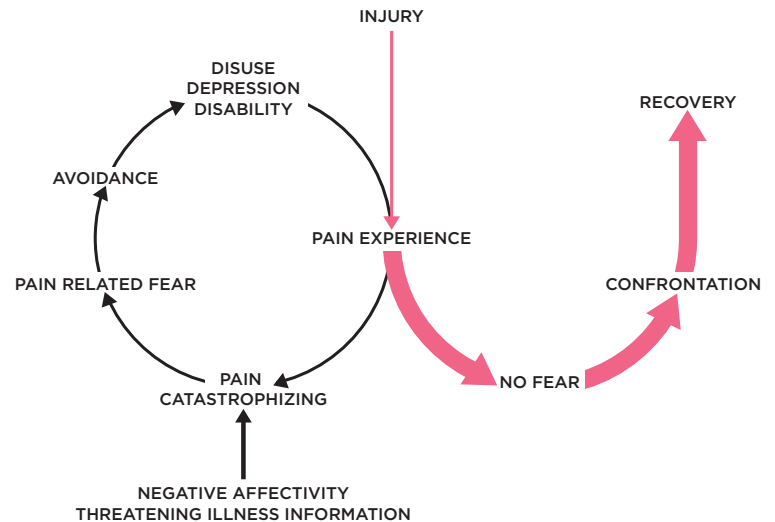


Some specific issues pertaining to PNE:

- Delivered primarily by physical therapists.<sup>28,33</sup>
- PNE is typically delivered in 15-30 minute sessions once or twice a week for 4-6 weeks.<sup>34-37</sup>
- The primary delivery method is verbal one-on-one education with the use of metaphors, examples, pictures and books.<sup>28,33</sup>
- PNE as an educational intervention is combined with various physical and movement-based therapies including exercise, and current best-evidence indicate that PNE plus movement/exercise is superior to educational-alone approaches in decreasing pain and disability.<sup>28,33</sup>
- Numbers needed to treat for PNE and chronic low back pain:
  - To improve function 2:1
  - To improve pain 3:1
  - ♦ In comparison Gabapentin's NNT is 6:1 for pain<sup>38</sup>

## Preemptive Pain Neuroscience Education

In regards to prevention, PNE is now being explored in acute and perioperative studies.<sup>11,39</sup> It is hypothesized that by educating patients more about the biology and physiology of a pain experience, they actually change seeking behaviors related to healthcare utilization.<sup>11</sup> For example, a recently developed preoperative PNE program was tested in a multi-center randomized clinical trial with 1 and 3 year outcomes.<sup>11,39,40</sup> One year after surgery; the group that received PNE had similar rates of pain and disability compared to the patients who did not receive PNE, but demonstrated a substantial reduction in postoperative medical utilization.<sup>11</sup> Despite having residual pain and disability, the PNE group spent 45% less on healthcare in the year following surgery compared to the non-PNE group.<sup>24</sup> A key element of the preoperative PNE was that pain after lumbar surgery was to be expected, normal, and over time would calm down.<sup>39</sup> On average, the PNE group spent over \$2000 less seeking help for their persistent pain and disability. In 2012, there were over 600,000 discectomies in the US alone and if the cost-savings per patient were to be applied to each person undergoing a discectomy in the US it would account for an annual savings of \$1.2 billion.<sup>9</sup> The results from the 1-year follow-up was sustained 2 years with publication of the 3-year outcome study. Upon completion of the preoperative PNE program for lumbar surgery, the same research team started trials on preoperative PNE for total knee arthroplasty and shoulder surgery.

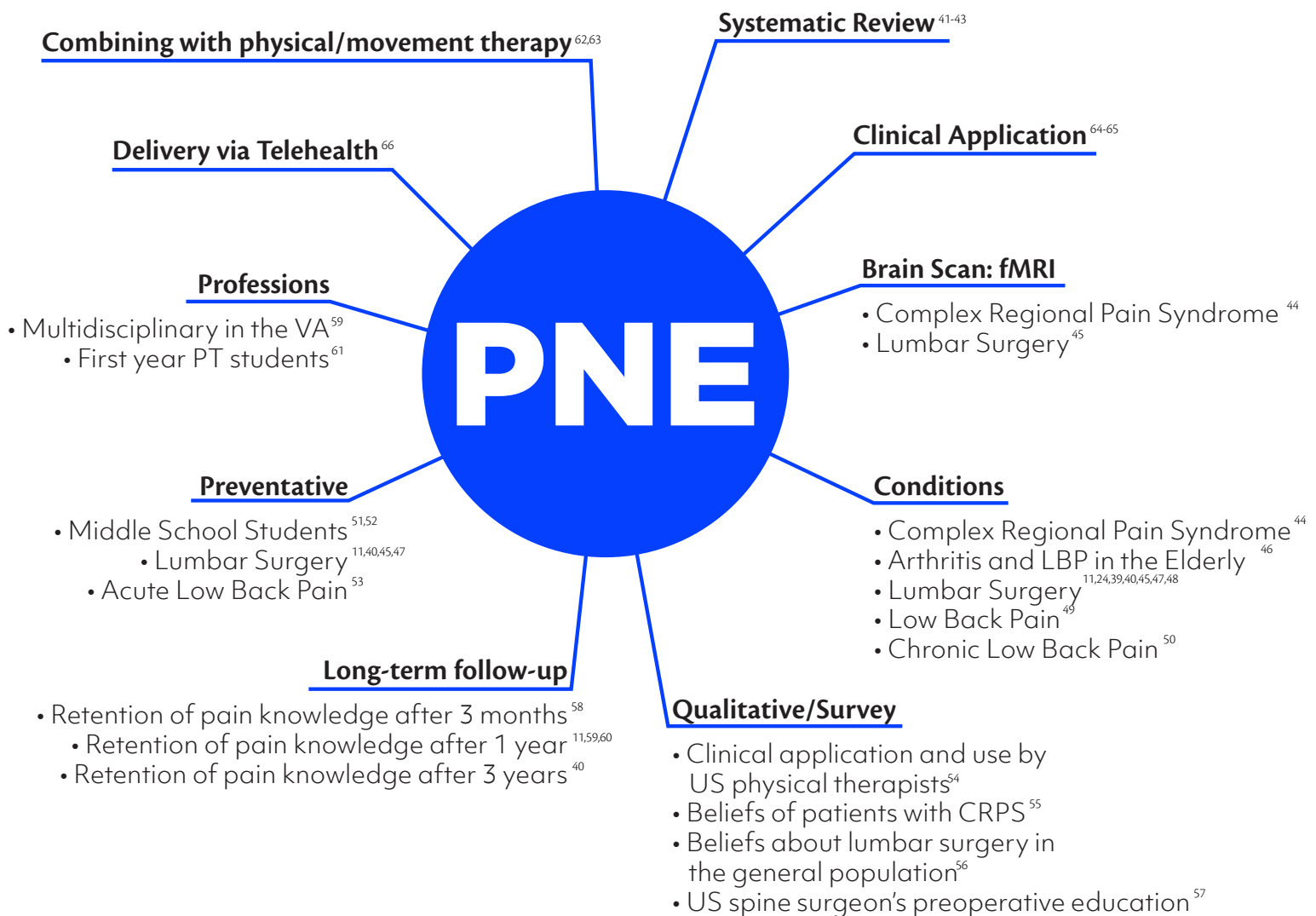


## Pain Neuroscience Education and Evidence in Motion

The following series of studies, pertaining to PNE has been conducted by the EIM research team:

- Adriaan Louw, PT, PhD
- Emilio "Louie" Puentedura, PT, DPT, PhD
- Ina Diener, PT, PhD
- Kory, Zimney, PT, DPT, PhD (c)
- Terry Cox, PT, DPT, PhD (c)
- Stephen G. Schmidt, PT, MSc (physio)

## References include published, accepted and submitted for publication studies:



## PNE and Behavior Change

Education by itself, however, is not a powerful facilitator of behavior change. In the words of the late Bill Fordyce:

*"Information is to behavior change as spaghetti is to a brick."*

The latest PNE systematic review demonstrated that when PNE is combined with a physical treatment (PNE+) is has superior results for pain reduction as compared to education alone.<sup>67</sup> The main idea of the + component of the PNE+ program is to utilize and add strategies aimed at overall well-being, facilitate movement, and increase function as well as enhancement of endogenous analgesia via non-pharmacological mechanisms.

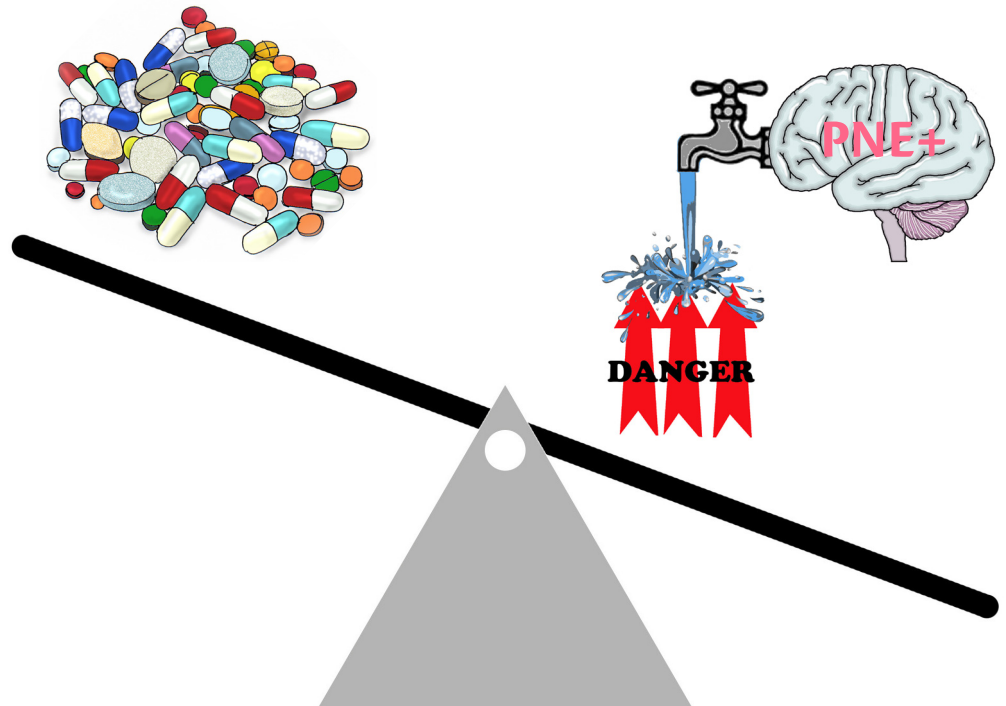
## Opioid Epidemic and the PNE+ Program

The current opioid epidemic prompts both the public and healthcare providers to ask, "What do we do?" As you read through the various components of the PNE+ approach, we want you to see it from the perspective of the opioid crisis. As a whole, the PNE+ program should be used as an alternative to the pharmaceutical delivery of opioids to treat pain. The various treatments we are describing have been studied extensively for their ability to turn on the non-pharmacological, naturally occurring endogenous systems, thus decreasing the need for medicine. The body of evidence in favor of the PNE+ approach versus the current use of opioids is staggering. Additionally, it can provide significant benefit with little to no side effects. It is proposed that the PNE+ program, as it's delivered and built into a patient's recovery, should coincide with the physician's tapering off the pain medication and thus be part of the anti-opioid initiative. Therapists need to study this following concept, know it well and propagate the idea:

The PNE+ program facilitates naturally occurring endogenous mechanisms, is far more powerful than the current pharmaceutical approach, and has little to no side effects. As the various aspects of the PNE+ program are applied, tapering of pharmaceuticals should occur per physician discretion.

The evidence? Below is a listing of various PNE+ components and evidence for engaging the various endogenous mechanisms. Collectively, this program demonstrates the relative efficacy of PNE+ over pharmaceutical opioids:

- PNE<sup>68-70</sup>
- Nutrition<sup>71-74</sup>
- Breathing<sup>75-77</sup>
- Biofeedback<sup>78-80</sup>
- Graded motor imagery<sup>81-83</sup>
- Safe, healing environment with compassion and empathy<sup>84-86</sup>
- Manual therapy<sup>87-89</sup>
- Neural mobilization<sup>90-92</sup>
- Modalities<sup>93-95</sup>
- Yoga<sup>96-98</sup>
- Relaxation and meditation<sup>76,99,100</sup>
- Aerobic exercise<sup>101-104</sup>
- Humor<sup>105-107</sup>
- Aquatic therapy<sup>108,109</sup>
- Social interaction<sup>110-112</sup>
- Coping skills<sup>113-115</sup>
- Sleep hygiene<sup>116-118</sup>
- Soft tissue/trigger point therapy<sup>119-121</sup>
- Stabilization and resistance training<sup>122-125</sup>
- Journaling<sup>126-128</sup>
- Stretches, movement and body awareness<sup>129,130</sup>
- Posture and position of power and confidence<sup>131,132</sup>



## Scientific Evidence:

1. Medicine Io. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC)2011.
2. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *The journal of pain : official journal of the American Pain Society.* Aug 2015;16(8):769-780.
3. Eccleston C, Malleson PN, Clinch J, Connell H, Sourbut C. Chronic pain in adolescents: evaluation of a programme of interdisciplinary cognitive behaviour therapy. *Arch Dis Child.* Oct 2003;88(10):881-885.
4. Eccleston C, Malleson P. Managing chronic pain in children and adolescents. We need to address the embarrassing lack of data for this common problem. *Bmj.* Jun 28 2003;326(7404):1408-1409.
5. Perquin CW, Hazebroek-Kampschreur AA, Hunfeld JA, et al. Pain in children and adolescents: a common experience. *Pain.* Jul 2000;87(1):51-58.
6. Paulozzi LJ. Prescription drug overdoses: a review. *J Safety Res.* Sep 2012;43(4):283-289.
7. Manchikanti L, Fellows B, Ailani H, Pampati V. Therapeutic use, abuse, and nonmedical use of opioids: a ten-year perspective. *Pain Physician.* Sep-Oct 2010;13(5):401-435.
8. Patrick SW, Fry CE, Jones TF, Buntin MB. Implementation Of Prescription Drug Monitoring Programs Associated With Reductions In Opioid-Related Death Rates. *Health Aff (Millwood).* Jun 22 2016.
9. Louw A, Puentedura EJ, Zimney K, Schmidt S. Know Pain, Know Gain? A Perspective on Pain Neuroscience Education in Physical Therapy. *J Orthop Sports Phys Ther.* Mar 2016;46(3):131-134.
10. Moseley GL. Reconceptualising pain according to modern pain sciences. *Physical Therapy Reviews.* 2007;12:169-178.
11. 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.* Aug 15 2014;39(18):1449-1457.
12. Nielsen M, Keefe FJ, Bennell K, Jull GA. Physical therapist-delivered cognitive-behavioral therapy: a qualitative study of physical therapists' perceptions and experiences. *Physical therapy.* Feb 2014;94(2):197-209.
13. Keefe FJ, Caldwell DS, Williams DA, et al. Pain coping skills training in the management of osteoarthritic knee pain: a comparative study. *Behaviour Therapy.* 1990;21:49-62.
14. Linton SJ. A review of psychological risk factors in back and neck pain. *Spine.* 2000;25:1148-1156.
15. Linton SJ, Nicholas M, MacDonald S. Development of a short form of the Orebro Musculoskeletal Pain Screening Questionnaire. *Spine.* Oct 15 2011;36(22):1891-1895.
16. Moseley GL. Unravelling the barriers to reconceptualisation of the problem in chronic pain: the actual and perceived ability of patients and health professionals to understand the neurophysiology. *The journal of pain : official journal of the American Pain Society.* 2003;4(4):184-189.
17. Haldeman S. Presidential address, North American Spine Society: failure of the pathology model to predict back pain. *Spine.* 1990;15(7):718-724.
18. Spielmann AL, Forster BB, Kokan P, Hawkins RH, Janzen DL. Shoulder after rotator cuff repair: MR imaging findings in asymptomatic individuals-initial experience. *Radiology.* Dec 1999;213(3):705-708.
19. Kjaer P, Leboeuf-Yde C, Korsholm L, Sorensen JS, Bendix T. Magnetic resonance imaging and low back pain in adults: a diagnostic imaging study of 40-year-old men and women. *Spine.* May 15 2005;30(10):1173-1180.
20. Linton SJ, Buer N, Vlaeyen J, Hellsing A-L. Are fear-avoidance beliefs related to the inception of an episode of back pain? A prospective study. *Psychology & health.* 2000/01/01/ 2000;14(6):1051-1059.
21. Vlaeyen JWS, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. *Pain.* 2000;85:317-322.
22. 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. *Manual therapy.* Apr 2013;18(2):96-102.
23. Greene DL, Appel AJ, Reinert SE, Palumbo MA. Lumbar disc herniation: evaluation of information on the internet. *Spine (Phila Pa 1976).* Apr 1 2005;30(7):826-829.
24. Louw A, Diener I, Puentedura E. Comparison of Terminology in Patient Education Booklets for Lumbar Surgery. *International Journal of Health Sciences.* 2014;2(3):47-56.
25. Gifford L. Aches and Pain. Cornwall: Wordpress; 2014.
26. Gifford L, Muncey H. Explaining Pain to Patients. Paper presented at: International Association on the Study of Pain1999; Vienna, Austria.
27. Moseley L. Combined physiotherapy and education is efficacious for chronic low back pain. *The Australian journal of physiotherapy.* 2002;48(4):297-302.
28. Louw A, Diener I, Butler DS, Puentedura EJ. The effect of neuroscience education on pain, disability, anxiety, and stress in chronic musculoskeletal pain. *Archives of physical medicine and rehabilitation.* Dec 2011;92(12):2041-2056.
29. Nijs J, Van Houdenhove B, Oostendorp RA. Recognition of central sensitization in patients with musculoskeletal pain: Application of pain neurophysiology in manual therapy practice. *Manual therapy.* Apr 2010;15(2):135-141.
30. Moseley GL, Butler DS. Fifteen Years of Explaining Pain: The Past, Present, and Future. *The journal of pain : official journal of the American Pain Society.* Jun 5 2015.
31. Moseley GL, Hodges PW, Nicholas MK. A randomized controlled trial of intensive neurophysiology education in chronic low back pain. *Clinical Journal of Pain.* 2004;20:324-330.
32. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain Physiology Education Improves Pain Beliefs in Patients With Chronic Fatigue Syndrome Compared With Pacing and Self-Management Education: A Double-Blind Randomized Controlled Trial. *Arch Phys Med Rehabil.* Aug 2010;91(8):1153-1159.
33. Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience education on musculoskeletal pain: A systematic review of the literature. *Physiother Theory Pract.* Jun 28 2016:1-24.
34. Meeus M, Nijs J, Van Oosterwijck J, Van Alsenoy V, Truijen S. Pain physiology education improves pain beliefs in patients with chronic fatigue syndrome compared with pacing and self-management education: a double-blind randomized controlled trial. *Archives of physical medicine and rehabilitation.* 2010;91(8):1153-1159.
35. 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.* Aug 15 2014;39(18):1449-1457.
36. Téllez-García M, de-la-Llave-Rincón AI, Salom-Moreno J, Palacios-Ceña M, Ortega-Santiago R, Fernández-de-las-Peñas 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.* 2014;19(3):464-472.
37. Van Oosterwijck J, Meeus M, Paul L, et al. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. *The Clinical journal of pain.* 2013;29(10):873-882.
38. Moore RA, Wiffen PJ, Derry S, Toelle T, Rice AS. Gabapentin for chronic neuropathic pain and fibromyalgia in adults. *The Cochrane database of systematic reviews.* 2014;4:CD007938.
39. Louw A, Butler DS, Diener I, Puentedura EJ. Development of a preoperative neuroscience educational program for patients with lumbar radiculopathy. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists.* May 2013;92(5):446-452.
40. Louw A, Diener I, Landers M, Zimney K, Puentedura E. Three-year follow-up of an RCT comparing preoperative pain neuroscience education for patients undergoing surgery for lumbar radiculopathy. *Journal of Spine Surgery.* 2017 - accepted for publication.
41. Louw A, Zimney K, Puentedura EJ, Diener I. The efficacy of pain neuroscience education on musculoskeletal pain: A systematic review of the literature. *Physiotherapy Theory and Practice.* Jul 2016;32(5):332-355.
42. Louw A, Diener I, Butler DS, Puentedura EJ. Preoperative education addressing postoperative pain in total joint arthroplasty: review of content and educational delivery methods. *Physiother Theory Pract.* Apr 2013;29(3):175-194.
43. Louw A, Puentedura EL, Mintken P. Use of an abbreviated neuroscience education approach in the treatment of chronic low back pain: A case report. *Physiother Theory Pract.* Jul 3 2011.
44. Fercho KA, Baugh LA, Louw A, Zimney K. Pain Neuroscience Education Effect on Pain Matrix Processing in an Individual with Complex Regional Pain Syndrome: A Single Subject Research Design. *European Pain Journal.* 2017 - Submitted for publication.



45. Louw A, Puentedura EJ, Diener I, Peoples RR. Preoperative therapeutic neuroscience education for lumbar radiculopathy: a single-case fMRI report. *Physiother Theory Pract.* Oct 2015;31(7):496-508.
46. Louw A, Zimney K, Johnson E, Kramer C, Fesler J, Burcham T. De-Educate to Re-Educate: Aging and Low Back Pain. *Aging Clin Exp Res.* 2017 - accepted for publication.
47. Louw A, Diener I, Puentedura EJ. The short term effects of preoperative neuroscience education for lumbar radiculopathy: A case series. *International Journal of Spine Surgery.* 2015;9:11.
48. Louw A, Louw Q, Crous LCC. Preoperative Education for Lumbar Surgery for Radiculopathy. *South African Journal of Physiotherapy.* July 2009 2009;65(2):3-8.
49. Ickmans K, Moens M, Putman K, et al. Back school or brain school for patients undergoing surgery for lumbar radiculopathy? Protocol for a randomised, controlled trial. *J Physiother.* Jul 2016;62(3):165.
50. Louw A, Puentedura EL, Mintken P. Use of an abbreviated neuroscience education approach in the treatment of chronic low back pain: a case report. *Physiother Theory Pract.* Jan 2012;28(1):50-62.
51. Louw A, Benz P, Podolak J, Zimney K, Wassinger CA. Pain Neuroscience Education for Middle School Kids and Fear of Physical Activity. *Physiotherapy 2017 - Submitted for Publication.*
52. Louw A, Podolak J, Zimney K, Schmidt S, Puentedura E. Can Pain Beliefs Change in Middle School Students? A Study of the Effectiveness of Pain Neuroscience Education. *Physiotherapy Theory and Practice.* 2017 - Accepted for publication.
53. Zimney K, Louw A, Puentedura EJ. Use of Therapeutic Neuroscience Education to address psychosocial factors associated with acute low back pain: a case report. *Physiother Theory Pract.* Apr 2014;30(3):202-209.
54. Louw A, Puentedura E, Zimney K, Cox T, Rico D. The Clinical Implementation of Pain Neuroscience Education: A Survey Study. *Physiother Theory Pract.* 2017 - accepted for publication.
55. Louw A, Zimney K, Cox T, O'Hotto C, Wassinger CA. The experiences and beliefs of patients with complex regional pain syndrome: An exploratory survey study. *Chronic illness.* Jan 01 2017;1742395317709329.
56. Landers MR, Puentedura E, Louw A, McCauley A, Rasmussen Z, Bungum T. A population-based survey of lumbar surgery beliefs in the United States. *Orthopedic nursing.* Jul-Aug 2014;33(4):207-216.
57. Louw A, Butler DS, Diener I, Puentedura EJ. Preoperative education for lumbar radiculopathy: A Survey of US Spine Surgeons. *International Journal of Spine Surgery.* 2012;6:130-139.
58. Louw A, Zimney K, Puentedura E. Retention of pain neuroscience knowledge: a multi-centre trial. *New Zealand Journal of Physiotherapy.* 2016;44(2):91-96.
59. Louw A, Vogsland R, Marth L, Marshall P, Landers M, Cox T. Pain Neuroscience Education across Healthcare Disciplines. *Archives of Physical Medicine and Rehabilitation.* 2017.
60. Louw A, Puentedura EJ, Diener I. A descriptive study of the utilization of physical therapy for postoperative rehabilitation in patients undergoing surgery for lumbar radiculopathy. *Eur Spine J.* Nov 2016;25(11):3550-3559.
61. Cox T, Puentedura E, Louw A. An Abbreviated Therapeutic Neuroscience Education Session Improves Pain Knowledge in First Year Physical Therapy Students But Does Not Change Attitudes or Beliefs *Journal of Manual & Manipulative Therapy.* 2017;25(1):11-21.
62. Louw A, Puentedura E, Nijs J. A Clinical Perspective on a Pain Neuroscience Education Approach to Manual Therapy. *Journal of Manual & Manipulative Therapy.* 2017.
63. Louw A, Farrell K, Landers M, et al. The Effect of Manual Therapy and Neuroplasticity Education on Chronic Low Back Pain: A Randomized Clinical Trial. *Journal of Manual & Manipulative Therapy.* 2016.
64. Louw A, Zimney K, O'Hotto C, Hilton S. The clinical application of teaching people about pain. *Physiother Theory Pract.* Jul 2016;32(5):385-395.
65. Diener I, Kargela M, Louw A. Listening is therapy: Patient interviewing from a pain science perspective. *Physiother Theory Pract.* Jul 2016;32(5):356-367.
66. Louw A. Therapeutic neuroscience education via e-mail: a case report. *Physiother Theory Pract.* Nov 2014;30(8):588-596.
67. Louw A, Zimney K, Puentedura EJ, Diener I. The Efficacy of Therapeutic Neuroscience Education on Musculoskeletal Pain – A Systematic Review of the Literature. *Physiother Theory Pract.* 2016;32(5):332-355.
68. Van Oosterwijck J, Meeus M, Paul L, et al. Pain physiology education improves health status and endogenous pain inhibition in fibromyalgia: a double-blind randomized controlled trial. *The Clinical journal of pain.* Oct 2013;29(10):873-882.
69. Moseley GL. A pain neuromatrix approach to patients with chronic pain. *Manual therapy.* Aug 2003;8(3):130-140.
70. Jensen KB, Kosek E, Wicksell R, et al. Cognitive Behavioral Therapy increases pain-evoked activation of the prefrontal cortex in patients with fibromyalgia. *Pain.* Jul 2012;153(7):1495-1503.
71. Spencer JP. Flavonoids and brain health: multiple effects underpinned by common mechanisms. *Genes & nutrition.* Dec 2009;4(4):243-250.
72. Dufresne CJ, Farnworth ER. A review of latest research findings on the health promotion properties of tea. *The Journal of nutritional biochemistry.* Jul 2001;12(7):404-421.
73. Tauler P, Aguilo A, Gimeno I, Fuentespina E, Tur JA, Pons A. Influence of vitamin C diet supplementation on endogenous antioxidant defences during exhaustive exercise. *Pflugers Archiv : European journal of physiology.* Sep 2003;446(6):658-664.
74. Butterfield D, Castegna A, Pocernich C, Drake J, Scapagnini G, Calabrese V. Nutritional approaches to combat oxidative stress in Alzheimer's disease. *The Journal of nutritional biochemistry.* Aug 2002;13(8):444.
75. Singh V, Wisniewski A, Britton J, Tattersfield A. Effect of yoga breathing exercises (pranayama) on airway reactivity in subjects with asthma. *Lancet.* Jun 9 1990;335(8702):1381-1383.
76. Kim SH, Schneider SM, Bevans M, et al. PTSD symptom reduction with mindfulness-based stretching and deep breathing exercise: randomized controlled clinical trial of efficacy. *The Journal of clinical endocrinology and metabolism.* Jul 2013;98(7):2984-2992.
77. Vassilakopoulos T, Roussos C, Zakynthinos S. The immune response to resistive breathing. *The European respiratory journal.* Dec 2004;24(6):1033-1043.
78. Rokicki LA, Holroyd KA, France CR, Lipchik GL, France JL, Kvaal SA. Change mechanisms associated with combined relaxation/EMG biofeedback training for chronic tension headache. *Applied psychophysiology and biofeedback.* Mar 1997;22(1):21-41.
79. deCharms RC, Maeda F, Glover GH, et al. Control over brain activation and pain learned by using real-time functional MRI. *Proceedings of the National Academy of Sciences of the United States of America.* Dec 20 2005;102(51):18626-18631.
80. Ciancarelli I, Tozzi-Ciancarelli MG, Spacca G, Di Massimo C, Carolei A. Relationship between biofeedback and oxidative stress in patients with chronic migraine. *Cephalalgia : an international journal of headache.* Oct 2007;27(10):1136-1141.
81. Moseley GL, Zalucki N, Birklein F, Marinus J, van Hilten JJ, Luomajoki H. Thinking about movement hurts: the effect of motor imagery on pain and swelling in people with chronic arm pain. *Arthritis and rheumatism.* May 15 2008;59(5):623-631.
82. Bowering KJ, O'Connell NE, Tabor A, et al. The effects of graded motor imagery and its components on chronic pain: a systematic review and meta-analysis. *The journal of pain : official journal of the American Pain Society.* Jan 2013;14(1):3-13.
83. Michielsen ME, Smits M, Ribbers GM, et al. The neuronal correlates of mirror therapy: an fMRI study on mirror induced visual illusions in patients with stroke. *J Neurol Neurosurg Psychiatry.* Apr 2011;82(4):393-398.
84. Van Ree JM, Niesink RJ, Van Wolfswinkel L, et al. Endogenous opioids and reward. *European journal of pharmacology.* Sep 29 2000;405(1-3):89-101.
85. Benedetti F, Amanzio M. The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. *Progress in neurobiology.* Jun 1997;52(2):109-125.
86. Fields HL. A motivation-decision model of pain: the role of opioids. Paper presented at: 11th World Congress on Pain 2006; Washington, USA.
87. Nijs J, Van Houdenhove B. From acute musculoskeletal pain to chronic widespread pain and fibromyalgia: application of pain neurophysiology in manual therapy practice. *Manual therapy.* Feb 2009;14(1):3-12.
88. Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Manual therapy.* Oct 2009;14(5):531-538.
89. Bialosky JE, Bishop MD, Robinson ME, Zeppieri G, Jr., George SZ. Spinal manipulative therapy has an immediate effect on thermal pain sensitivity in people with low back pain: a randomized controlled trial. *Physical therapy.* Dec 2009;89(12):1292-1303.

90. Santos FM, Silva JT, Giardini AC, et al. Neural mobilization reverses behavioral and cellular changes that characterize neuropathic pain in rats. *Molecular pain*. 2012;8:57.
91. Santos FM, Grecco LH, Pereira MG, et al. The neural mobilization technique modulates the expression of endogenous opioids in the periaqueductal gray and improves muscle strength and mobility in rats with neuropathic pain. *Behavioral and brain functions* : BBF. May 13 2014;10:19.
92. Beneciuk JM, Bishop MD, George SZ. Effects of upper extremity neural mobilization on thermal pain sensitivity: a sham-controlled study in asymptomatic participants. *J Orthop Sports Phys Ther*. Jun 2009;39(6):428-438.
93. Bender T, Nagy G, Barna I, Tefner I, Kadas E, Geher P. The effect of physical therapy on beta-endorphin levels. *European journal of applied physiology*. Jul 2007;100(4):371-382.
94. Wright A, Sluka KA. Nonpharmacological treatments for musculoskeletal pain. *The Clinical journal of pain*. Mar 2001;17(1):33-46.
95. Sabino GS, Santos CM, Francisci JN, de Resende MA. Release of endogenous opioids following transcatheter electric nerve stimulation in an experimental model of acute inflammatory pain. *The journal of pain* : official journal of the American Pain Society. Feb 2008;9(2):157-163.
96. Sengupta P. Health Impacts of Yoga and Pranayama: A State-of-the-Art Review. *International journal of preventive medicine*. Jul 2012;3(7):444-458.
97. Kulkarni DD, Bera TK. Yogic exercises and health--a psycho-neuro immunological approach. *Indian journal of physiology and pharmacology*. Jan-Mar 2009;53(1):3-15.
98. Sharma M, Lingam VC, Nahar VK. A systematic review of yoga interventions as integrative treatment in breast cancer. *Journal of cancer research and clinical oncology*. Dec 2016;142(12):2523-2540.
99. Zeidan F, Emerson NM, Farris SR, et al. Mindfulness Meditation-Based Pain Relief Employs Different Neural Mechanisms Than Placebo and Sham Mindfulness Meditation-Induced Analgesia. *The Journal of neuroscience* : the official journal of the Society for Neuroscience. Nov 18 2015;35(46):15307-15325.
100. Sharon H, Maron-Katz A, Ben Simon E, et al. Mindfulness Meditation Modulates Pain Through Endogenous Opioids. *Am J Med*. Jul 2016;129(7):755-758.
101. Esch T, Stefano GB. Endogenous reward mechanisms and their importance in stress reduction, exercise and the brain. *Archives of medical science* : AMS. Jun 30 2010;6(3):447-455.
102. Koltyn KF. Analgesia following exercise: a review. *Sports Med*. Feb 2000;29(2):85-98.
103. O'Connor PJ, Cook DB. Exercise and pain: the neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. *Exerc Sport Sci Rev*. 1999;27:119-166.
104. Naugle KM, Fillingim RB, Riley JL, 3rd. A meta-analytic review of the hypoalgesic effects of exercise. *The journal of pain* : official journal of the American Pain Society. Dec 2012;13(12):1139-1150.
105. Martin RA. Humor, laughter, and physical health: methodological issues and research findings. *Psychological bulletin*. Jul 2001;127(4):504-519.
106. Berk LS, Felten DL, Tan SA, Bittman BB, Westengard J. Modulation of neuroimmune parameters during the eustress of humor-associated mirthful laughter. *Alternative therapies in health and medicine*. Mar 2001;7(2):62-72, 74-66.
107. Finan PH, Garland EL. The role of positive affect in pain and its treatment. *The Clinical journal of pain*. Feb 2015;31(2):177-187.
108. Mazzardo-Martins L, Martins DF, Marcon R, et al. High-intensity extended swimming exercise reduces pain-related behavior in mice: involvement of endogenous opioids and the serotonergic system. *The journal of pain* : official journal of the American Pain Society. Dec 2010;11(12):1384-1393.
109. Becker BE. Aquatic therapy: scientific foundations and clinical rehabilitation applications. *PM & R* : the journal of injury, function, and rehabilitation. Sep 2009;1(9):859-872.
110. Karelina K, DeVries AC. Modeling social influences on human health. *Psychosomatic medicine*. Jan 2011;73(1):67-74.
111. Lopez-Martinez AE, Esteve-Zarazaga R, Ramirez-Maestre C. Perceived social support and coping responses are independent variables explaining pain adjustment among chronic pain patients. *The journal of pain* : official journal of the American Pain Society. Apr 2008;9(4):373-379.
112. Krahe C, Springer A, Weinman JA, Fotopoulou A. The social modulation of pain: others as predictive signals of salience - a systematic review. *Frontiers in human neuroscience*. 2013;7:386.
113. Bandura A, Cioffi D, Taylor CB, Brouillard ME. Perceived self-efficacy in coping with cognitive stressors and opioid activation. *Journal of personality and social psychology*. Sep 1988;55(3):479-488.
114. Hebb AL, Poulin JF, Roach SP, Zacharko RM, Drolet G. Cholecystokinin and endogenous opioid peptides: interactive influence on pain, cognition, and emotion. *Progress in neuro-psychopharmacology & biological psychiatry*. Dec 2005;29(8):1225-1238.
115. Goodin BR, McGuire L, Allshouse M, et al. Associations between catastrophizing and endogenous pain-inhibitory processes: sex differences. *The journal of pain* : official journal of the American Pain Society. Feb 2009;10(2):180-190.
116. Smith MT, Quartana PJ, Okonkwo RM, Nasir A. Mechanisms by which sleep disturbance contributes to osteoarthritis pain: a conceptual model. *Current pain and headache reports*. Dec 2009;13(6):447-454.
117. Menefee LA, Cohen MJ, Anderson WR, Doghramji K, Frank ED, Lee H. Sleep disturbance and nonmalignant chronic pain: a comprehensive review of the literature. *Pain medicine*. Jun 2000;1(2):156-172.
118. Edwards RR, Grace E, Peterson S, Klick B, Haythornthwaite JA, Smith MT. Sleep continuity and architecture: associations with pain-inhibitory processes in patients with temporomandibular joint disorder. *European journal of pain (London, England)*. Nov 2009;13(10):1043-1047.
119. Goats GC, Keir KA. Connective tissue massage. *British journal of sports medicine*. Sep 1991;25(3):131-133.
120. Frey Law LA, Evans S, Knudtson J, Nus S, Scholl K, Sluka KA. Massage reduces pain perception and hyperalgesia in experimental muscle pain: a randomized, controlled trial. *The journal of pain* : official journal of the American Pain Society. Aug 2008;9(8):714-721.
121. Ireland M, Olson M. Massage therapy and therapeutic touch in children: state of the science. *Alternative therapies in health and medicine*. Sep 2000;6(5):54-63.
122. Kraemer WJ, Ratamess NA, French DN. Resistance training for health and performance. *Curr Sports Med Rep*. Jun 2002;1(3):165-171.
123. Kraemer WJ, Aguilera BA, Terada M, et al. Responses of IGF-I to endogenous increases in growth hormone after heavy-resistance exercise. *J Appl Physiol* (1985). Oct 1995;79(4):1310-1315.
124. Fuentes CJ, Armijo-Olivo S, Magee DJ, Gross DP. Effects of exercise therapy on endogenous pain-relieving peptides in musculoskeletal pain: a systematic review. *The Clinical journal of pain*. May 2011;27(4):365-374.
125. Ambrose KR, Golightly YM. Physical exercise as non-pharmacological treatment of chronic pain: Why and when. *Best Pract Res Clin Rheumatol*. Feb 2015;29(1):120-130.
126. Bruhl S, Chung OY, Burns JW. Anger expression and pain: an overview of findings and possible mechanisms. *Journal of behavioral medicine*. Dec 2006;29(6):593-606.
127. Wright JG, Chung OY. Mastery or mystery? Therapeutic writing: A Review of the Literature. *British Journal of Guidance and Counseling*. 2001;29(3):277-291.
128. Baikie KA, Wilhelm K. Emotional and physical health benefits of expressive writing. *Advances in psychiatric treatment*. 2005;11(5):338-346.
129. da Costa BR, Vieira ER. Stretching to reduce work-related musculoskeletal disorders: a systematic review. *Journal of rehabilitation medicine*. May 2008;40(5):321-328.
130. Hodges PW, Smeets RJ. Interaction between pain, movement, and physical activity: short-term benefits, long-term consequences, and targets for treatment. *The Clinical journal of pain*. Feb 2015;31(2):97-107.
131. Bohns VK, Wiltermuth SS. It hurts when I do this (or you do that): Posture and pain tolerance. *Journal of Experimental Social Psychology*. 2012;48(1):341-345.
132. Carney DR, Cuddy AJ, Yap AJ. Power posing: brief nonverbal displays affect neuroendocrine levels and risk tolerance. *Psychological science*. Oct 2010;21(10):1363-1368.