Regional interdependence and manual therapy directed at the thoracic spine

Amy McDevitt¹, Jodi Young², Paul Mintken¹, Josh Cleland²

¹University of Colorado, School of Medicine, Physical Therapy Program, Anschutz Medical Campus, Aurora, CO, USA, ²Franklin Pierce University, Physical Therapy Program, Concord, NH, USA

Thoracic spine manipulation is commonly used by physical therapists for the management of patients with upper quarter pain syndromes. The theoretical construct for using thoracic manipulation for upper quarter conditions is a mainstay of a regional interdependence (RI) approach. The RI concept is likely much more complex and is perhaps driven by a neurophysiological response including those related to peripheral, spinal cord and supraspinal mechanisms. Recent evidence suggests that thoracic spine manipulation results in neurophysiological changes, which may lead to improved pain and outcomes in individuals with musculoskeletal disorders. The intent of this narrative review is to describe the research supporting the RI concept and its application to the treatment of individuals with neck and/or shoulder pain. Treatment utilizing both thrust and non-thrust thoracic manipulation has been shown to result in improvements in pain, range of motion and disability in patients with upper quarter conditions. Research has yet to determine optimal dosage, techniques or patient populations to which the RI approach should be applied; however, emerging evidence supporting a neurophysiological effect for thoracic spine manipulation may negate the need to fully answer this question. Certainly, there is a need for further research examining both the clinical efficacy and effectiveness of manual therapy interventions utilized in the RI model as well as the neurophysiological effects resulting from this intervention.

Keywords: Thoracic manipulation, Regional interdependence, Physical therapy, Thoracic spine, Manual therapy, Neck, Shoulder

Regional Interdependence

Thoracic spine manipulation is commonly used by physical therapists for the management of patients with neck and upper extremity pain syndromes. The theoretical construct for thoracic manipulation and its mechanism of action has traditionally been described as regional interdependence (RI). Regional interdependence has been defined by Wainner *et al.*¹ as the 'concept that seemingly unrelated impairments in a remote anatomical region may contribute to, or be associated with, the patient's primary complaint'. The authors originally described this as a mechanism solely functioning within the musculoskeletal system. However, Bialosky *et al.*² argued that the RI concept is likely much more complex and could also be driven by a neurophysiological response including those related to peripheral mechanisms, spinal cord mechanisms or supraspinal mechanisms. More recently, the RI concept has been further refined by Suecki *et al.*³ as 'the concept that a patient's primary musculoskeletal symptom(s) may be directly or indirectly

related or influenced by impairments from various body regions and systems regardless of proximity to the primary symptom(s)'. This implies that impairments impacting one's musculoskeletal system may be greatly impacted through other systems, such as the peripheral and central nervous systems, via a neurophysiological or biopsychosocial response.

Descriptions of RI can be found in the literature for ~40 years, even prior to the coining of the familiar term, 'RI'. In 1976, Murray-Leslie and Wright⁴ found that individuals who had carpal tunnel syndrome exhibited narrowing of the intervertebral discs of the cervical spine relative to the vertebral bodies. Furthermore, in 1976, Gunn and Milbrandt⁵ reported on the use of interventions directed to the cervical spine in individuals with tennis elbow. A majority of individuals who received intervention at the cervical spine experienced relief of distal symptoms. Early evidence of a relationship between the lumbar spine and lower extremities has also been documented. Cibulka *et al.*⁶ indicated the connection between passive hip internal and external range of motion (ROM) and sacroiliac joint pain. In more recent years, evidence has emerged demonstrating the effectiveness of utilizing manual therapy techniques that incorporate the concept of RI in various diagnoses,

Correspondence to: Amy McDevitt, 13121 E. 17th Avenue, Mail Stop C244, University of Colorado Anschutz Medical Campus, Aurora, CO 80045, USA. Email: amy.mcdevitt@ucdenver.edu

including spinal stenosis,⁷ knee osteoarthritis⁸ and patellofemoral syndrome.⁹ All of these studies found significantly greater improvements in patients who received manual therapy interventions both proximal and distal to the patients' primary symptoms. However, the main body of physical therapy literature using an RI approach describes treating the thoracic spine, often for individuals with neck pain and/or shoulder pain.^{10–18} The outcomes resulting from utilizing thoracic spine manipulation for individuals with neck pain and shoulder dysfunction have been very promising for reducing pain, increasing ROM and improving function.^{10–18}

Mechanisms of Manual Therapy

Bialosky *et al.*¹⁹ have proposed a model that identifies two categories of potential mechanisms by which manual therapy techniques exert their biomechanical and neurophysiological effects (Fig. 1). Biomechanical links can be made between different anatomical regions and concurrent symptoms such as the thoracic spine facet joint and referral of pain to the neck and shoulder.²⁰ However, emerging evidence suggests that the neurophysiological effects of manual therapy play an important role, and it is likely that there is a complex inter-relationship between biomechanical and neurophysiological effects occurring in RI.¹⁹ The interplay

between these theoretical mechanisms may maximize patient outcomes when the clinician includes treating anatomical areas sometimes remote from the site of the patient's symptoms. In addition, it is important to recognize that a third factor may come into play which is beyond the scope of the current manuscript; for example, outcomes may be further influenced by interaction between these effects combined with other non-specific factors including patient specific psychosocial factors and patient expectation.

Neurophysiological effects can be further sub-classified as peripheral, spinal and supraspinal mechanisms.¹⁹ Injuries to the musculoskeletal system may result in biochemical alterations in the periphery that may impact multiple body systems and initiate an inflammatory cascade. Preliminary evidence suggests that manual therapy techniques might have an influence on biochemical activity and perhaps even mediate the inflammatory process. A study by McPartland *et al.*²¹ demonstrated that manual therapy resulted in the production of endogenous cannabinoids when compared with a placebo. Another study found that thoracic manipulation reduced inflammatory cytokines in the short term.²² Recently, Plaza-Manzano *et al.*²³ randomly assigned individuals to either cervical manipulation, thoracic manipulation or control group. Both the

Figure Key: The model suggests a transient, mechanical stimulus to the tissue produces a chain of neurophysiological effects. Solid arrows denote a direct mediating effect. Broken arrows denote an associative relationship which may include:

-----> = an association between a construct and its measure

Bold boxes indicate the measurement of a construct

ACC = anterior cingulate cortex; PAG = periaqueductal gray; RVM = rostral ventromedial medulla

Figure 1 Mechanisms of manual therapy comprehensive model.¹⁹

cervical and thoracic spine manipulation groups experienced higher levels in neurotensin and the cervical manipulation group also experienced significantly greater increases in cortisol, suggesting that manipulation may positively influence biochemical processes.

Mechanisms associated with spinal cord activity may potentially be associated with hypoalgesia or altered motor neuron pool activity. For example, studies have demonstrated that spinal manipulation results in increased pressure pain thresholds in individuals with mechanical neck pain²⁴ and increased thermal pain thresholds in asymptomatic individuals²⁵ and in patients with low back pain.^{26,27} Dishman and Burke²⁷ demonstrated that both cervical and lumbar manipulation may potentially alter motor neuron excitability.

Manual therapy has also been shown to exert effects on supraspinal structures and processes, including pain processing centres²⁸ as well as endocrine and autonomic responses.¹⁹ Using functional magnetic resonance imaging (fMRI) to measure cerebral haemodynamics, a recent case series by Sparks *et al.*²⁹ found thoracic spine manipulation resulted in reduced cerebral blood flow, as measured by the blood oxygenation level-dependent response, to areas associated with the pain matrix (insular cortex) in individuals with experimentally induced pain. In addition, the participants exhibited decreased subjective pain scores on the numeric pain rating scale. A recent systematic review found that all seven of the randomized clinical trials reported an increase in sympathetic nervous system activity, as measured by heart rate, respiratory rate, blood pressure or skin conductance following manual therapy.³⁰ It should be recognized the aforementioned studies were all performed on asymptomatic individuals; therefore further research is needed to determine if these neurophysiological mechanisms occur with manual therapy when applied to individuals with musculoskeletal disorders and pain.

Thoracic Manipulation and Neck Pain

Thoracic spine manipulation for the treatment of neck pain has historically been thought to have less risk over cervical spine manipulation. Specifically, Masaracchio *et al.*³¹ suggest that clinicians have more commonly chosen to target the thoracic spine with manipulation instead of the cervical spine because of the controversy surrounding the perceived safety of cervical manipulation. Consequently, numerous studies have focused on the use of thoracic spine manipulation versus cervical spine manipulation for treating individuals with neck pain.^{13–15,31–36} In contrast, it has been suggested that cervical thrust manipulation may carry a more significant risk of vertebrobasilar artery injury and some purport that the benefits do not outweigh the risks³⁷ despite

research showing overall risk of complications to be low and potentially preventable.^{38–40}

Several studies have utilized thoracic manipulation as an intervention on its own,^{33,41–44} compared it to another intervention or used it in conjunction with an alternate intervention.^{31,32,34,35,45–49}

For those trials that compared thoracic manipulation to another intervention, the comparison intervention varied. In a randomized clinical trial, Cleland *et al.*³² compared the outcomes of a group of patients with mechanical neck pain receiving thoracic spine manipulation versus non-thrust manipulation. The results demonstrated that those who received manipulation experienced significantly greater improvements in pain and disability over those receiving non-thrust manipulation at short-term follow-up. Suvarnnato *et al.*⁴⁴ also compared manipulation versus non-thrust manipulation and reported significant differences in pain and ROM immediately and 24 hours after intervention. One additional study compared supine thoracic manipulation to a placebo manipulation and those in the experimental group experienced an immediate and statistically significant reduction in pain.¹⁴ Puentedura *et al.*⁵⁰ and Martinez-Segura *et al.*⁵¹ compared thoracic manipulation to cervical manipulation. The results of these two studies varied, with Puentedura *et al.*⁵⁰ reporting statistically significant greater improvements in pain reduction and decreased neck disability with cervical manipulation whereas Martinez-Segura *et al.*⁵¹ showed similar reductions in pain for both the cervical and thoracic manipulation groups.

Several studies have examined the effects of thoracic manipulation in conjunction with alternative types of intervention, which is more reflective of clinical practice. Four of the studies combined thoracic manipulation with the use of modalities.^{34,35,45,46} Savolainen *et al.*⁴⁸ used thoracic manipulation and a standard exercise program and in Cleland *et al.*'s¹³ derivation of a clinical prediction rule included thoracic manipulation and a home exercise programme for cervical active ROM. Saavedra-Hernández *et al.*⁴⁹ and Dunning *et al.*⁴⁷ looked at the combined use of cervical and thoracic manipulations, whereas Masaracchio *et al.*³¹ examined the use of thoracic manipulation and cervical non-thrust manipulation compared to only cervical non-thrust manipulation. All of the studies^{31,32,34,35,45–47} utilizing adjunct interventions combined with thoracic manipulation (multimodal approach) found statistically significant greater improvement and/or clinically meaningful differences for pain and disability scores. Five of the studies also found statistically significant differences in ROM measurements after intervention.^{34,35,45–47}

Studies that have examined the effects of thoracic spine manipulation for individuals with neck pain

have included a variety of technique positions, including supine, seated or prone, (Figs. 2 and 3) with limited evidence to suggest which specific thoracic manipulation technique is most effective. Karas and Hunt⁴² and Casanova-Mendez *et al.*⁴³ both recently studied the use of specifically targeted thoracic manipulation techniques. Karas and Hunt⁴² compared the effects of a seated thoracic manipulation to a targeted supine thoracic technique.

Figure 2 Supine middle thoracic spine thrust manipulation technique. The therapist uses her body to push down through the individual's arms to perform a high-velocity, low-amplitude thrust directed towards T5 through T8.

Figure 3 Prone middle to lower thoracic spine thrust manipulation technique. The therapist achieves a 'skin lock' with the pisiforms of each hand over the transverse processes of the target vertebra pushing caudal with one hand and cephalad with the other. The therapist then uses her body to push down through her arms to perform a high-velocity, low-amplitude posterior to anterior thrust.

Those who received a targeted supine thoracic manipulation had statistically greater improvements in pain over those receiving a seated thoracic manipulation. In the Casanova-Mendez *et al.*⁴³ study, a supine technique was compared to a prone technique and those receiving the prone technique had statistically greater improvements in cervical extension, right cervical side flexion and left cervical rotation. Overall, there is a large body of evidence supporting the use of thoracic manipulation via the RI approach for treating patients with neck pain.

Thoracic Manipulation and Shoulder Pain

In addition to treating mechanical neck pain, thoracic manipulation is a popular management strategy in treating patients with shoulder pain. According to a number of sources, of patients with a complaint of shoulder pain, more than 40% had associated impairment of the cervicothoracic spine and adjacent ribs.^{52–57} In addition Sobel *et al.*^{52,53} postulated that dysfunction in these adjacent areas may be a primary cause of some patients' shoulder pain. Furthermore, impairment of the cervicothoracic spine and ribs may increase an individual's risk of developing neck-shoulder pain and may contribute to an overall worse prognosis.^{10,52,54–56} The rationale for using thoracic spine manual therapy in individuals with shoulder pain has some face validity because of the increased prevalence of reduced mobility of the upper thoracic spine in these individuals.^{52,55,56,58} Furthermore, a study by Crosbie⁵⁹ highlighted the inter-relationship between the thoracic spine and arm elevation, further supporting the concept that thoracic spine hypomobility may impair shoulder mechanics and ultimately patient function.

The RI model of Wainner *et al.*¹ suggests that treating the thoracic spine in individuals with shoulder pain is warranted, and several research studies support this treatment approach.^{10–12} Studies have examined techniques directed at the thoracic spine to treat primary shoulder pain,^{10,12,60} shoulder impingement^{11,58,61,62} and rotator cuff tendinopathy.⁶³ In a recent study by Haik *et al.*,⁵⁸ individuals with shoulder impingement syndrome (SIS) had an immediate decrease in pain following a treatment of thoracic spine manipulation.

Studies investigating the use of thoracic spine manipulation for the treatment of shoulder pain have demonstrated improvement in shoulder pain, disability and shoulder ROM.^{11,12,58,63} A long-term follow-up study of patients with a primary report of shoulder pain found, at the follow-up periods of 12, 26 and 52 weeks, that the group that received manipulative therapy (UMC_MT) to the cervicothoracic spine and rib cage in addition to usual medical care (UMC) from their primary physician reported significantly greater improvements in severity of pain and disability,

and demonstrated higher rates of perceived 'full recovery' than a group that solely received UMC.¹⁰ A study by Winters *et al.*⁶⁴ investigated the use of manipulation, physiotherapy (exercise therapy, massage and physical modalities, excluding the use of thrust or non-thrust manipulation) and corticosteroid for the treatment of shoulder complaints. Patients were grouped into a 'shoulder girdle group' (pain and decreased movement proposed to originate from the cervical or thoracic spine and ribs) or the 'synovial group' (shoulder pain originating from subacromial, acromioclavicular or glenohumeral regions). The results of the study found that, in the shoulder girdle group, manipulation was superior to physiotherapy with 70% of patients in the manipulation group considering themselves cured.⁶⁴ This suggests that there may exist a subgroup of individuals with shoulder pain that experience a dramatic response from thoracic manipulation.¹²

Additional effects on the shoulder girdle region after thoracic manipulation include increased middle trapezius activity in individuals with rotator cuff tendinopathy⁶³ and increased lower trapezius strength in asymptomatic individuals.⁶⁵ While scapular muscle strength may improve following thoracic manual therapy, changes in scapulohumeral rhythm and mechanics were not found to change significantly after application of thoracic manipulative interventions.^{58,63,66} These results further support a neurophysiological effect, as opposed to a local biomechanical effect.⁶⁷ One could argue that this improved muscle function gives health care providers a therapeutic window to maximize therapeutic exercise interventions.

Future Areas of Study

Certainly, there is a need for more research examining the clinical effectiveness of manual therapy interventions utilized in the RI model. It is also important to continue to examine the mechanisms of spinal manipulation as well as the interactions between the non-specific, neurophysiological and local mechanical effects. Although the RI approach of using thoracic manipulation for the management of neck and shoulder pain has shown positive outcomes, many of the aforementioned studies only assess immediate, short-term outcomes.^{14,41-43,45,51} Few studies have followed patients for longer time frames, such as 12 months.⁴⁸ When considering the existing body of knowledge in this area, some important questions remain. How long do these effects actually last? What is the optimal dosage required? How many treatment sessions are appropriate to maximize patient response? Are there subgroups of patients who will respond more favourably? What treatments constitute the ideal 'combined' treatment approach?

Most clinical trials investigating specific interventions attempt to answer an explanatory question: Under ideal

circumstances, can a certain intervention in ideal patients improve patients' outcomes?⁶⁸ These explanatory, or prescriptive, trials explore efficacy and may be useful to expert clinicians with highly compliant patients but do not necessarily represent clinical reality. Pragmatic trials, on the other hand, ask a broader, more clinically relevant question: Does this intervention improve patient specific outcomes when applied by typical clinicians to typical patients? The goal of the pragmatic trial is to explore the effectiveness of a treatment in the 'real,' clinical world. In other words, prescriptive trials explore whether a given treatment works under ideal circumstances while pragmatic trials explore whether the treatment provides benefit under actual clinical practice circumstances. To this end, prescriptive trials frequently have strict inclusion and exclusion criteria to decrease the likelihood that extraneous factors, such as medical conditions, will impact the outcomes.⁶⁹ Pragmatic trials usually attempt to be as inclusive as possible to increase the generalizability of the outcomes. As the clinic is not an 'ideal' world, and most of the patients the authors treat are not 'ideal' patients, the authors would argue that research in the area of thoracic manual therapy should shift to more pragmatic designs. In the clinic, the application of manual therapy includes the patient's feedback and modifications of multiple factors based on this feedback coupled with patient response. In a pragmatic trial, the researchers are not concerned with how an intervention works compared to a control, but they are simply interested in whether it works or not. Much of the research that has been conducted showing the clinical benefits of thoracic spine manual therapy has been prescriptive in nature, and several studies comparing low-velocity non-thrust manipulation to high-velocity manipulation have suggested that high-velocity techniques are superior to low velocity.^{32,47} Cook *et al.*⁷⁰ argue that these outcomes may be because, in part, of the fact that the low-velocity techniques were prescriptively used, which is dissimilar to how the techniques are applied in clinical practice. In a recent systematic review of 14 studies by Young *et al.*¹⁷ looking at thoracic non-thrust manipulation versus thrust manipulation, the authors reported that there were improvements in pain, ROM and disability with the use of either technique, but they did not report if the studies were more pragmatic or prescriptive in nature. Future research should be conducted to directly compare the use of thoracic manipulation versus non-thrust manipulation and the use of pragmatic versus prescriptive applications of thoracic spine manual therapy in the treatment of musculoskeletal disorders.

Future studies should also include long-term follow-up since the majority of the studies in the literature only examined short-term outcomes. Ideally, researchers should strive to use multicentre, pragmatic, randomized controlled study designs

with multiple treating clinicians to make the research more clinically applicable, generalizable and representative of the patients that we treat. Future studies should also investigate the effects of specific thoracic manipulation techniques, as many studies utilize ‘manual therapy packages’ which precludes the ability to determine if one technique is superior to another. In addition, future studies of the neurophysiological and non-specific effects of thoracic manipulation should investigate changes over multiple sessions and take into account a patient’s desire for pain relief.⁷¹ Finally, continued research is needed to determine the ideal number of treatment sessions and the most effective dosage of the various manipulative techniques.

Summary

As we have illustrated above, Wainner *et al.*’s¹ model of RI seems to have some validity in the physical therapy management of musculoskeletal conditions based on published research. This model seems particularly suitable to the application of manual therapy to the thoracic spine given the emerging evidence supporting a neurophysiological effect for this intervention.^{19,28,29,72,73} Given the reported lack of accuracy and specificity of manual therapy techniques,^{74–76} it seems even more plausible that the reported positive effects can be explained by non-specific and neurophysiological mechanisms. A systematic review by Coronado *et al.*⁷⁷ concluded that manipulation is likely a non-specific technique acting on the pain modulating system, even though the exact mechanisms remain elusive. It is clear that neurophysiological effects occur following manual therapy, and that these effects are not necessarily specific to the region to which they are applied.^{19,67,78–80} Hypoalgesia following manual therapy has been reported in regions distant from the application.^{36,51,67,81} As described earlier, fMRI findings from a study by Sparks *et al.*²⁹ marks a considerable paradigm shift in manual therapy clinical decision making. Rather than using manual therapy to treat a localized biomechanical impairment, today’s clinician, armed with current best evidence, may decide to treat a patient with shoulder pain using thoracic manipulation based on a well-documented neurophysiological effect, as opposed to a local biomechanical effect. This decision would be weighed more heavily towards current best evidence over examination findings from clinical tests and measures that are limited by questionable reliability and validity.^{82,83} In addition, non-specific mechanisms, such as the placebo response and patient expectation, have been shown to have a significant effect on outcomes.^{71,84–87} As clinicians, we should embrace these findings to ultimately improve our treatment outcomes.

Disclaimer Statements

Contributors All authors contributed to the writing of the paper.

Funding None.

Conflicts of interest The authors declare no conflict of interest.

Ethics approval None required.

References

- 1 Wainner RS, Whitman JM, Cleland JA, Flynn TW. Regional interdependence: a musculoskeletal examination model whose time has come. *J Orthop Sports Phys Ther.* 2007;37(11):658–60.
- 2 Bialosky JE, Bishop MD, George SZ. Regional interdependence: a musculoskeletal examination model whose time has come. *J Orthop Sports Phys Ther.* 2008;38(3):159–160, [author reply 160].
- 3 Sueki DG, Cleland JA, Wainner RS. A regional interdependence model of musculoskeletal dysfunction: research, mechanisms, and clinical implications. *J Man Manip Ther.* 2013;21(2):90–102.
- 4 Murray-Leslie CF, Wright V. Carpal tunnel syndrome, humeral epicondylitis, and the cervical spine: a study of clinical and dimensional relations. *Br Med J.* 1976;1(6023):1439–42.
- 5 Gunn CC, Milbrandt WE. Tennis elbow and the cervical spine. *Can Med Assoc J.* 1976;114(9):803–9.
- 6 Cibulka MT, Sinacore DR, Cromer GS, Delitto A. Unilateral hip rotation range of motion asymmetry in patients with sacroiliac joint regional pain. *Spine (Phila Pa 1976).* 1998;23(9):1009–15.
- 7 Whitman JM, Flynn TW, Childs JD, Wainner RS, Gill HE, Ryder MG, *et al.* A comparison between two physical therapy treatment programs for patients with lumbar spinal stenosis: a randomized clinical trial. *Spine.* 2006;31(22):2541–9.
- 8 Deyle GD, Henderson NE, Matekel RL, Ryder MG, Garber MB, Allison SC. Effectiveness of manual physical therapy and exercise in osteoarthritis of the knee. A randomized, controlled trial. *Ann Intern Med.* 2000;132(3):173–81.
- 9 Iverson CA, Sutlive TG, Crowell MS, Morrell RL, Perkins MW, Garber MB, *et al.* Lumbopelvic manipulation for the treatment of patients with patellofemoral pain syndrome: development of a clinical prediction rule. *J Orthop Sports Phys Ther.* 2008;38(6):297–309, [discussion 309–12].
- 10 Bergman GJ, Winters JC, Groenier KH, Pool JJ, Meyboom-de Jong B, K, *et al.* Manipulative therapy in addition to usual medical care for patients with shoulder dysfunction and pain: a randomized, controlled trial. *Ann Intern Med.* 2004;141(6):432–9.
- 11 Boyles RE, Ritland BM, Miracle BM, Barclay DM, Faul MS, Moore JH, *et al.* The short-term effects of thoracic spine thrust manipulation on patients with shoulder impingement syndrome. *Man Ther.* 2009;14(4):375–80.
- 12 Mintken PE, Cleland JA, Carpenter KJ, Bieniek ML, Keirns M, Whitman JM. Some factors predict successful short-term outcomes in individuals with shoulder pain receiving cervicothoracic manipulation: a single-arm trial. *Phys Ther.* 2010;90(1):26–42.
- 13 Cleland JA, Childs JD, Fritz JM, Whitman JM, Eberhart SL. Development of a clinical prediction rule for guiding treatment of a subgroup of patients with neck pain: use of thoracic spine manipulation, exercise, and patient education. *Phys Ther.* 2007;87(1):9–23.
- 14 Cleland JA, Childs JD, McRae M, Palmer JA, Stowell T. Immediate effects of thoracic manipulation in patients with neck pain: a randomized clinical trial. *Man Ther.* 2005;10(2):127–35.
- 15 Cleland JA, Mintken PE, Carpenter K, Fritz JM, Glynn P, Whitman J, *et al.* Examination of a clinical prediction rule to identify patients with neck pain likely to benefit from thoracic spine thrust manipulation and a general cervical range of motion exercise: multi-center randomized clinical trial. *Phys Ther.* 2010;90(9):1239–50.
- 16 Cross KM, Kuenze C, Grindstaff TL, Hertel J. Thoracic spine thrust manipulation improves pain, range of motion, and self-reported function in patients with mechanical neck pain: a systematic review. *J Orthop Sports Phys Ther.* 2011;41(9):633–42.

- 17 Young JL, Walker D, Snyder S, Daly K. Thoracic manipulation versus mobilization in patients with mechanical neck pain: a systematic review. *J Man Manip Ther.* 2014;22(3):141–53.
- 18 Walser RF, Meserve BB, Boucher TR. The effectiveness of thoracic spine manipulation for the management of musculoskeletal conditions: a systematic review and meta-analysis of randomized clinical trials. *J Man Manip Ther.* 2009;17(4):237–46.
- 19 Bialosky JE, Bishop MD, Price DD, Robinson ME, George SZ. The mechanisms of manual therapy in the treatment of musculoskeletal pain: a comprehensive model. *Man Ther.* 2009;14(5):531–8.
- 20 Fukui S, Ohseto K, Shiotani M. Patterns of pain induced by distending the thoracic zygapophyseal joints. *Reg Anesth.* 1997;22(4):332–6.
- 21 McPartland JM, Giuffrida A, King J, Skinner E, Scotter J, Musty RE. Cannabimimetic effects of osteopathic manipulative treatment. *J Am Osteopath Assoc.* 2005;105(6):283–91.
- 22 Teodorczyk-Injeyan JA, Injeyan HS, Ruegg R. Spinal manipulative therapy reduces inflammatory cytokines but not substance P production in normal subjects. *J Manipulative Physiol Ther.* 2006;29(1):14–21.
- 23 Plaza-Manzano G, Molina-Ortega F, Lomas-Vega R, Martinez-Amat A, Achalandabaso A, Hita-Contreras F. Changes in biochemical markers of pain perception and stress response after spinal manipulation. *J Orthop Sports Phys Ther.* 2014;44(4):231–9.
- 24 de Camargo VM, Albuquerque-Sendin F, Berzin F, Stefanelli VC, de Souza DP, Fernandez-de-las-Penas C. Immediate effects on electromyographic activity and pressure pain thresholds after a cervical manipulation in mechanical neck pain: a randomized controlled trial. *J Manipulative Physiol Ther.* 2011;34(4):211–20.
- 25 Dishman JD, Greco DS, Burke JR. Motor-evoked potentials recorded from lumbar erector spinae muscles: a study of corticospinal excitability changes associated with spinal manipulation. *J Manipulative Physiol Ther.* 2008;31(4):258–70.
- 26 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. *Phys Ther.* 2009;89(12):1292–303.
- 27 Dishman JD, Burke J. Spinal reflex excitability changes after cervical and lumbar spinal manipulation: a comparative study. *Spine J.* 2003;3(3):204–12.
- 28 Bialosky JE, George SZ, Horn ME, Price DD, Staud R, Robinson ME. Spinal manipulative therapy-specific changes in pain sensitivity in individuals with low back pain (NCT01168999). *J Pain.* 2014;15(2):136–48.
- 29 Sparks C, Cleland JA, Elliott JM, Zagardo M, Liu WC. Using functional magnetic resonance imaging to determine if cerebral hemodynamic responses to pain change following thoracic spine thrust manipulation in healthy individuals. *J Orthop Sports Phys Ther.* 2013;43(5):340–8.
- 30 Kingston L, Claydon L, Tumilty S. The effects of spinal mobilizations on the sympathetic nervous system: a systematic review. *Man Ther.* 2014;19(4):281–7.
- 31 Masaracchio M, Cleland JA, Hellman M, Hagins M. Short-term combined effects of thoracic spine thrust manipulation and cervical spine nonthrust manipulation in individuals with mechanical neck pain: a randomized clinical trial. *J Orthop Sports Phys Ther.* 2013;43(3):118–27.
- 32 Cleland JA, Glynn P, Whitman JM, Eberhart SL, MacDonald C, Childs JD. Short-term effects of thrust versus nonthrust mobilization/manipulation directed at the thoracic spine in patients with neck pain: a randomized clinical trial. *Phys Ther.* 2007;87(4):431–40.
- 33 Fernandez-de-las-Penas C, Palomeque-del-Cerro L, Rodriguez-Blanco C, Gomez-Conesa A, Miangolarra-Page JC. Changes in neck pain and active range of motion after a single thoracic spine manipulation in subjects presenting with mechanical neck pain: a case series. *J Manipulative Physiol Ther.* 2007;30(4):312–20.
- 34 Gonzalez-Iglesias J, Fernandez-de-las-Penas C, Cleland JA, Albuquerque-Sendin F, Palomeque-del-Cerro L, Mendez-Sanchez R. Inclusion of thoracic spine thrust manipulation into an electro-therapy/thermal program for the management of patients with acute mechanical neck pain: a randomized clinical trial. *Man Ther.* 2009;14(3):306–13.
- 35 Gonzalez-Iglesias J, Fernandez-de-las-Penas C, Cleland JA, Gutierrez-Vega Mdel R. Thoracic spine manipulation for the management of patients with neck pain: a randomized clinical trial. *J Orthop Sports Phys Ther.* 2009;39(1):20–7.
- 36 Salom-Moreno J, Ortega-Santiago R, Cleland JA, Palacios-Cena M, Truyols-Dominguez S, Fernandez-de-las-Penas C. Immediate changes in neck pain intensity and widespread pressure pain sensitivity in patients with bilateral chronic mechanical neck pain: a randomized controlled trial of thoracic thrust manipulation vs non-thrust mobilization. *J Manipulative Physiol Ther.* 2014;37(5):312–9.
- 37 Di Fabio RP. Manipulation of the cervical spine: risks and benefits. *Phys Ther.* 1999;79(1):50–65.
- 38 Haldeman S, Kohlbeck FJ, McGregor M. Unpredictability of cerebrovascular ischemia associated with cervical spine manipulation therapy: a review of sixty-four cases after cervical spine manipulation. *Spine (Phila Pa 1976).* 2002;27(1):49–55.
- 39 Hurwitz EL, Morgenstern H, Vassilaki M, Chiang LM. Adverse reactions to chiropractic treatment and their effects on satisfaction and clinical outcomes among patients enrolled in the UCLA Neck Pain Study. *J Manipulative Physiol Ther.* 2004;27(1):16–25.
- 40 Puentedura EJ, March J, Anders J, Perez A, Landers MR, Wallmann HW, et al. Safety of cervical spine manipulation: are adverse events preventable and are manipulations being performed appropriately? A review of 134 case reports. *J Man Manip Ther.* 2012;20(2):66–74.
- 41 Krauss J, Creighton D, Ely JD, Podlowska-Ely J. The immediate effects of upper thoracic translational spinal manipulation on cervical pain and range of motion: a randomized clinical trial. *J Man Manip Ther.* 2008;16(2):93–9.
- 42 Karas S, Olson Hunt MJ. A randomized clinical trial to compare the immediate effects of seated thoracic manipulation and targeted supine thoracic manipulation on cervical spine flexion range of motion and pain. *J Man Manip Ther.* 2014;22(2):108–14.
- 43 Casanova-Mendez A, Oliva-Pascual-Vaca A, Rodriguez-Blanco C, Heredia-Rizo AM, Gogorza-Arroitaonandia K, Almazan-Campos G. Comparative short-term effects of two thoracic spinal manipulation techniques in subjects with chronic mechanical neck pain: a randomized controlled trial. *Man Ther.* 2014;19(4):331–7.
- 44 Suvarnnato T, Puntumetakul R, Kaber D, Boucaut R, Boonphakob Y, Arayawichanon P, et al. The effects of thoracic manipulation versus mobilization for chronic neck pain: a randomized controlled trial pilot study. *J Phys Ther Sci.* 2013;25(7):865–71.
- 45 Fernandez-De-Las-Penas C, Cleland JA, Huijbregts P, Palomeque-Del-Cerro L, Gonzalez-Iglesias J. Repeated applications of thoracic spine thrust manipulation do not lead to tolerance in patients presenting with acute mechanical neck pain: a secondary analysis. *J Man Manip Ther.* 2009;17(3):154–62.
- 46 Lau HM, Wing Chiu TT, Lam TH. The effectiveness of thoracic manipulation on patients with chronic mechanical neck pain – a randomized controlled trial. *Man Ther.* 2011;16(2):141–7.
- 47 Dunning JR, Cleland JA, Waldrop MA, Arnot CF, Young IA, Turner M, et al. Upper cervical and upper thoracic thrust manipulation versus nonthrust mobilization in patients with mechanical neck pain: a multicenter randomized clinical trial. *J Orthop Sports Phys Ther.* 2012;42(1):5–18.
- 48 Savolainen A, Ahlberg J, Nummala H, Nissinen M. Active or passive treatment for neck-shoulder pain in occupational health care? A randomized controlled trial. *Occup Med (Lond).* 2004;54(6):422–4.
- 49 Saavedra-Hernández M, Arroyo-Morales M, Cantarero-Villanueva I, Fernández-Lao C, Castro-Sánchez AM, Puentedura EJ, et al. Short-term effects of spinal thrust joint manipulation in patients with chronic neck pain: a randomized clinical trial. *Clin Rehabil.* 2013;27(6):504–12.
- 50 Puentedura EJ, Landers MR, Cleland JA, Mintken PE, Huijbregts P, Fernandez-de-las-Penas C. Thoracic spine thrust manipulation versus cervical spine thrust manipulation in patients with acute neck pain: a randomized clinical trial. *J Orthop Sports Phys Ther.* 2011;41(4):208–20.
- 51 Martinez-Segura R, De-la-Llave-Rincon AI, Ortega-Santiago R, Cleland JA, Fernandez-de-Las-Penas C. Immediate changes in widespread pressure pain sensitivity, neck pain, and cervical range of motion after cervical or thoracic thrust manipulation in patients with bilateral chronic mechanical neck pain: a randomized clinical trial. *J Orthop Sports Phys Ther.* 2012;42(9):806–14.

- 52 Sobel JS, Kremer I, Winters JC, Arendzen JH, de Jong BM. The influence of the mobility in the cervicothoracic spine and the upper ribs (shoulder girdle) on the mobility of the scapulohumeral joint. *J Manipulative Physiol Ther.* 1996;19(7):469–74.
- 53 Sobel JS, Winters JC, Groenier K, Arendzen JH, Meyboom de Jong B. Physical examination of the cervical spine and shoulder girdle in patients with shoulder complaints. *J Manipulative Physiol Ther.* 1997;20(4):257–62.
- 54 Norlander S, Aste-Norlander U, Nordgren B, Sahlstedt B. Mobility in the cervico-thoracic motion segment: an indicative factor of musculo-skeletal neck-shoulder pain. *Scand J Rehabil Med.* 1996;28(4):183–92.
- 55 Norlander S, Gustavsson BA, Lindell J, Nordgren B. Reduced mobility in the cervico-thoracic motion segment – a risk factor for musculoskeletal neck-shoulder pain: a two-year prospective follow-up study. *Scand J Rehabil Med.* 1997;29(3):167–74.
- 56 Norlander S, Nordgren B. Clinical symptoms related to musculoskeletal neck-shoulder pain and mobility in the cervico-thoracic spine. *Scand J Rehabil Med.* 1998;30(4):243–51.
- 57 Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. *Pain.* 2003;102(1–2):167–78.
- 58 Haik MN, Albuquerque-Sendin F, Silva CZ, Siqueira-Junior AL, Ribeiro IL, Camargo PR. Scapular kinematics pre- and post-thoracic thrust manipulation in individuals with and without shoulder impingement symptoms: a randomized controlled study. *J Orthop Sports Phys Ther.* 2014;44(7):475–87.
- 59 Crosbie J, Kilbreath SL, Hollmann L, York S. Scapulohumeral rhythm and associated spinal motion. *Clin Biomech.* 2008;23(2):184–92.
- 60 Strunce JB, Walker MJ, Boyles RE, Young BA. The immediate effects of thoracic spine and rib manipulation on subjects with primary complaints of shoulder pain. *J Man Manip Ther.* 2009;17(4):230–6.
- 61 Bang MD, Deyle GD. Comparison of supervised exercise with and without manual physical therapy for patients with shoulder impingement syndrome. *J Orthop Sports Phys Ther.* 2000;30(3):126–37.
- 62 Tate AR, McClure PW, Young IA, Salvatori R, Michener LA. Comprehensive impairment-based exercise and manual therapy intervention for patients with subacromial impingement syndrome: a case series. *J Orthop Sports Phys Ther.* 2010;40(8):474–93.
- 63 Muth S, Barbe MF, Lauer R, McClure PW. The effects of thoracic spine manipulation in subjects with signs of rotator cuff tendinopathy. *J Orthop Sports Phys Ther.* 2012;42(12):1005–16.
- 64 Winters JC, Sobel JS, Groenier KH, Arendzen HJ, Meyboom-de Jong B. Comparison of physiotherapy, manipulation, and corticosteroid injection for treating shoulder complaints in general practice: randomised, single blind study. *BMJ.* 1997;314(7090):1320–5.
- 65 Cleland J, Selleck B, Stowell T, Browne L, Alberini S, St Cyr H, et al. Short-term effects of thoracic manipulation on lower trapezius muscle strength. *J Man Manip Ther.* 2004;12(2):82–90, [31 ref].
- 66 Rosa DP, Albuquerque-Sendin F, Salvini TF, Camargo PR. Effect of seated thoracic manipulation on changes in scapular kinematics and scapulohumeral rhythm in young asymptomatic participants: a randomized study. *J Manipulative Physiol Ther.* 2013;36(8):546–54.
- 67 George SZ, Bishop MD, Bialosky JE, Zepieri G Jr, Robinson ME. Immediate effects of spinal manipulation on thermal pain sensitivity: an experimental study. *BMC Musculoskelet Disord.* 2006;7:68.
- 68 Sackett DL. Explanatory and pragmatic clinical trials: a primer and application to a recent asthma trial. *Pol Arch Med Wewn.* 2011;121(7–8):259–63.
- 69 Godwin M, Ruhland L, Casson I, MacDonald S, Delva D, Birtwhistle R, et al. Pragmatic controlled clinical trials in primary care: the struggle between external and internal validity. *BMC Med Res Methodol.* 2003;3:28.
- 70 Cook C, Learman K, Showalter C, Kabbaz V, O'Halloran B. Early use of thrust manipulation versus non-thrust manipulation: a randomized clinical trial. *Man Ther.* 2013;18(3):191–8.
- 71 Bialosky JE, Bishop MD, Robinson ME, Barabas JA, George SZ. The influence of expectation on spinal manipulation induced hypoalgesia: an experimental study in normal subjects. *BMC Musculoskelet Disord.* 2008;9:19.
- 72 Bialosky JE, George SZ, Bishop MD. How spinal manipulative therapy works: why ask why? *J Orthop Sports Phys Ther.* 2008;38(6):293–5.
- 73 Bialosky JE, Simon CB, Bishop MD, George SZ. Basis for spinal manipulative therapy: a physical therapist perspective. *J Electromyogr Kinesiol.* 2012;22(5):643–7.
- 74 Chiradejnant A, Maher CG, Latimer J, Stepanovitch N. Efficacy of 'therapist-selected' versus 'randomly selected mobilisation techniques for the treatment of low back pain: a randomised controlled trial. *Aust J Physiother.* 2003;49(4):233–41.
- 75 Ross JK, Bereznick DE, McGill SM. Determining cavitation location during lumbar and thoracic spinal manipulation: is spinal manipulation accurate and specific? *Spine.* 2004;29(13):1452–7.
- 76 Kent P, Marks D, Pearson W, Keating J. Does clinician treatment choice improve the outcomes of manual therapy for non-specific low back pain? A metaanalysis. *J Manipulative Physiol Ther.* 2005;28(5):312–22.
- 77 Coronado RA, Gay CW, Bialosky JE, Carnaby GD, Bishop MD, George SZ. Changes in pain sensitivity following spinal manipulation: a systematic review and meta-analysis. *J Electromyogr Kinesiol.* 2012;22(5):752–67.
- 78 Wright A. Hypoalgesia post-manipulative therapy: a review of a potential neurophysiological mechanism. *Man Ther.* 1995;1(1):11–16.
- 79 Colloca CJ, Keller TS, Gunzburg R. Neuromechanical characterization of in vivo lumbar spinal manipulation. Part II. Neurophysiological response. *J Manipulative Physiol Ther.* 2003;26(9):579–91.
- 80 Pickar JG. Neurophysiological effects of spinal manipulation. *Spine J.* 2002;2(5):357–71.
- 81 Vicenzino B, Collins D, Benson H, Wright A. An investigation of the interrelationship between manipulative therapy-induced hypoalgesia and sympathoexcitation. *J Manipulative Physiol Ther.* 1998;21(7):448–53.
- 82 Cleland JA, Childs JD, Fritz JM, Whitman JM. Interrater reliability of the history and physical examination in patients with mechanical neck pain. *Arch Phys Med Rehabil.* 2006;87(10):1388–95.
- 83 Potter L, McCarthy C, Oldham J. Intraexaminer reliability of identifying a dysfunctional segment in the thoracic and lumbar spine. *J Manipulative Physiol Ther.* 2006;29(3):203–7.
- 84 Bialosky JE, Bishop MD, Cleland JA. Individual expectation: an overlooked, but pertinent, factor in the treatment of individuals experiencing musculoskeletal pain. *Phys Ther.* 2010;90(9):1345–55.
- 85 Bialosky JE, Bishop MD, George SZ, Robinson ME. Placebo response to manual therapy: something out of nothing? *J Man Manip Ther.* 2011;19(1):11–19.
- 86 Bishop MD, Bialosky JE, Cleland JA. Patient expectations of benefit from common interventions for low back pain and effects on outcome: secondary analysis of a clinical trial of manual therapy interventions. *J Man Manip Ther.* 2011;19(1):20–5.
- 87 Bishop MD, Mintken PE, Bialosky JE, Cleland JA. Patient expectations of benefit from interventions for neck pain and resulting influence on outcomes. *J Orthop Sports Phys Ther.* 2013;43(7):457–65.