Skew-symmetric Random Effect Models with Application to a Preventive Cohort Study: Improving Outcomes in Low Back Pain Patients

Marjan Mansourian, Zahra Mahdiyeh[1], Jongbae J Park[2], Shaghayegh Haghjooyejavanmard[3]

Department of Biostatistics and Epidemiology, Health School, and Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [1]Department of Statistics, University of Isfahan, Isfahan, Iran, [2]Department of Physical Medicine and Rehabilitation, Asian Medicine and Acupuncture Research, School of Medicine, University of North Carolina, USA, [3]Department of physiology, Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.

Correspondence to:
Associate Prof. Shaghayegh Haghjooy Javanmard Applied Physiology Research Center, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: sh_haghjoo@med.mui.ac.ir

Date of Submission: Jul 11, 2012

Date of Acceptance: Oct 09, 2012

How to cite this article: Mansourian M, Mahdiyeh Z, Park JJ, Haghjooyejavanmard S. Skew-symmetric Random Effect Models with Application to a Preventive Cohort Study: Improving Outcomes in Low Back Pain Patients. Int J Prev Med.2013;4:279-85.

ABSTRACT

Background: To investigate the respective contribution of various biologic and psychosocial factors, especially Health Related Quality of Life (HRQOL) as a main outcome, in the natural history of acute low back pain (LBP) and to evaluate the impact of this condition on HRQOL.

Methods: In a prospective cohort study For 24 weeks, 150 patients were assessed at an outpatient clinic in Korea consulting for low back and confirmed disc herniation duration at inclusion and treated with treatment package comprised of herbal medicines, acupuncture, bee venom acupuncture, and a Korean version of spinal manipulation (Chuna). Study participants were evaluated at baseline and every 4 weeks for 24 weeks. Low back intensity levels were measured on a visual analog scale (0-10), back function was evaluated with the Oswestry Disability Index (0-100), disability assessed by HRQOL assessed by the short form 36 health survey (0-100 in 8 different sub-categories).

Results: Out of 150 patients, 128 completed the 24 weeks of traditional therapy. Patients reported improvements SF-36 outcome measures. At the completion of the study, low back pain scores improved by a mean of 3.3 (95% CI = 2.8 to 3.8). According to the results of our modeling, low back intensity level, back function and BMI measures had significant effects on quality of life during study. Interpreting the coefficients of modeling, the impact of the decreasing acute LBP episode on HRQOL by VAS and ODI outcomes, was high and important.

Conclusions: This study highlights the large contribution of integrative package therapy as an effective preventive method for improving LBP patient's HRQOL.

Keywords: Low back pain, health related quality of life, oswestry disability index

Original Article

INTRODUCTION

Low back pain (LBP) which has risen in most industrialized countries is one of the most frequent reasons both, for consulting a primary care physician and for taking time off

routine activities.[1] Long term sickness absence, is associated with serious health risks, and future serious illness.[2] Low back pain disorder affects 80% of the population at some time of them life,[3] and corresponding costs led to important researches, concerning determinants, preventive exercises, and treatments.[4] Studies showed that, having previous history of LBP is often prognostic of future back problems.[5] Chronic cases of this problem which represent decreased muscle flexibility and trunk strength led to significant burden on the health care and compensation systems.[6]

Perhaps, prevention of LBP in primary stages, contribute to prevention of disabilities of back pain in progressive stages.[7,8]

Some indicative health instrument would be useful to explore health related quality of life (HRQOL) in relation to LBP.[9,10] HRQOL measurement instruments have been developed to evaluate health status and its components, such as physical activity, psychological functioning (emotional and mental activity), social functioning (relationships with others and participation in social activities), perception of health status, and pain.[11] These measurements have been widely used to evaluate the broad impact of various diseases on patients and the effectiveness of different conditions and also to be related to the extent of satisfaction with care associated with various treatments.[11] The documentation of factors predictive of a developed impact of LBP on HRQOL would be of great value for defining management strategies.[12]

Although LBP tends to increase over time, for many people it becomes chronic, requiring different interventions. Surgery can be effective where there is a clearly recognized structural pathology that is possible to be the cause of the pain[13] but, chronic LBP may exist without having an identifiable structural pathology.

Considering the costs, risks and distresses associated with surgery methods and the indistinct results, surgery is often considered as the last treatment option for LBP.

Many patients search for non-surgical conservative treatment at clinics where both modern procedures and integrative treatments are available.

In many Asian countries, the traditional system of medicine has developed in to a more integrative systems consist of herbal medicine[14] spinal manipulation,[15] bee venom acupuncture,[16] and acupuncture.[17]

We report this study, using up dated statistical modeling to evaluate the impact of acute LBP on HRQOL and determine the contributions of physical and psychosocial factors to the LBP recovery adjusted by some probable confounders, according to 24 weeks carefully followed, a preventive cohort of patients with LBP traditional treated.

METHODS

Patients and interventions

One hundred and fifty consecutive patients aged 18 years and older, self-referring to (i.e. first consultation with) for a primary complaint of LBP or had referred with lumbar disc herniation already confirmed by MRI, between November 2006 and October 2007 at Jaseng Hospital in Korea, which offers both, Western and Korean medical services. Of the 150 patients who were registered in the study, 116 had sub-acute or chronic LBP, and 34 experienced acute LBP. These recruited patients had not been previously treated for LBP at this hospital. Exclusion criteria were having LBP caused by non-spinal or soft tissue problems, VAS of pain 4 or less, pregnancy, spinal tumor, rheumatoid arthritis, unexplained weight loss; and major organ transplantation.

The therapeutic package consisted of weekly treatments and daily intake of herbal medicine for 24 weeks. Treatments included: 20 min sessions of acupuncture,[18,19] 20 min sessions of a Korean version of spinal manipulation known as Chuna,[20] bee venom acupuncture 20 min at physician's discretion,[17] and special herbal medicines in dry powder form and water extracted form as prescribed by attending physicians from the 10 herbal medicines 2 g and 120 ml, respectively, twice a day, 30 min after meal.[21] We considered the following as independent variables: Visual analogue scale[22] (VAS,0-10) of back pain and leg pain, while the Oswestry Disability Index[23] (ODI), sex, age and BMI. SF-36 Health Related Quality of Life Questionnaire[24,25] was secondary outcomes was assessed as response variable. The time dependent variables were evaluated at baseline, 4th, 8th, 12th, 16th, 20th, and 24th week as longitudinal form.

Statistical molding description

A skew-symmetric random intercept mixed model was used to take into account the intra-patient and inter-patient variability in an outcome attributable to repeated measurements and to allow the inclusion of patients with missing values.

The skew-symmetric models as alternative to the normal model can be applied in application where the symmetry seems unreasonable.[26-30] Thus, the construction of asymmetric distributions can accommodate practical values of skewness and kurtosis can be useful for data modeling and robustness studies of normal theory methods.

For the purpose of inference, we used the Bayesian Markov chain Monte Carlo (MCMC) approach that provides a comparatively simple numerical tool that finds a solution as analytical difficulties inherent in the ML approach. To perform the skew-modeling, we mainly focus on some elliptical family, such as normal and Student's t distributions, as well as the skew form of these densities as the skew-symmetric families of distributions for the random intercept. In the Bayesian framework, this is equivalent to the two-stage hierarchy form. These Bayesian hierarchical models, equivalent to the two-stage hierarchy form, for the data analysis based on McMC techniques. The estimated random intercepts distribution according to the normal model by the estimated plots clearly showed deviation from normality in such a way that the distribution of intercept shows evidence of skewness. The goodness of fit between different models is evaluated by Bayesian model selection criteria. Model fitting was implemented by OpenBugs free software (www.ime.usp.br/mbranco).

The results of modeling determining the effect of traditional treatment on quality of life variable by considering VAS, ODI, age, sex, surgery recommended status, baseline HRQOL measures and BMI between different follow-ups. For each time-dependent variable, we analyzed the difference between the measurements obtained at the six time points.

RESULTS

The patients were 34.7 ± 8.4 years old (mean ± standard deviation). 58.4% of patients were male. The number of patients who had normal BMI category (18.5-23), overweight (>23), obesity and underweight (<18.5) was 63 (42%), 37 (24.7%) and 48 (32%), respectively. 61.3% from total subjects have recommended for surgery. Figure 1 show ODI and VAS levels (as two important factors which can show the effect of the traditional treatment), over time for 25 randomly selected subjects and suggests that ODI and VAS have uncertain trend over time for selected subjects.

Based on BUGS codes used for fitting different models, we use 10, 000 iterations after discarding the first 5, 000 iterations to make inference. To avoid correlation problems in the generated chains,

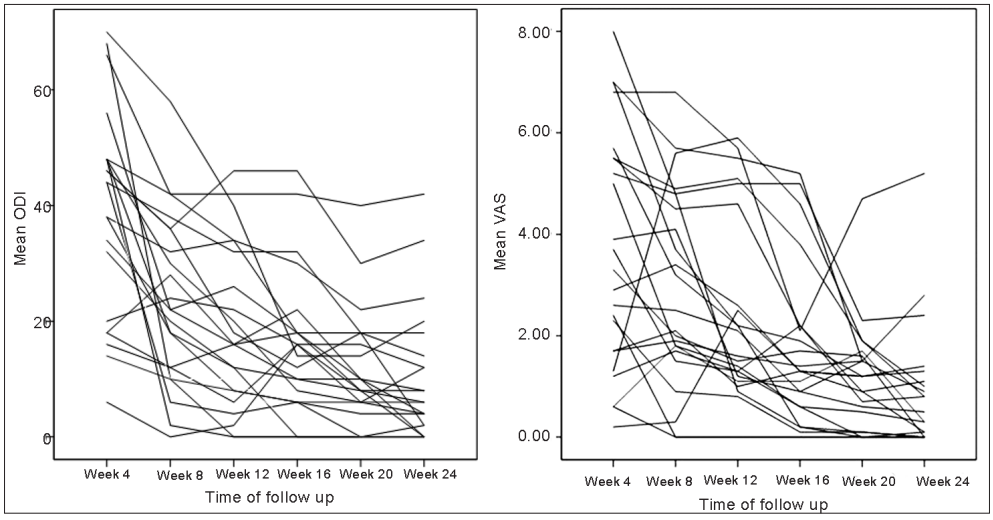

Figure 1: Mean of response variables over time scale for the low back pain cohort study. Visual analogue scale of back pain (right), and oswestry disability index (left)

the lag value was set to 5. Resulting parameter estimates (posterior means). According to the best model based on Bayesian model selection criteria (skew-normal random intercept model), VAS and ODI measures, age and BMI were significant based on the 95% Bayesian probability intervals in skew-symmetric modeling also, based on insignificant coefficients, there was no significant difference in HRQOL measures between different genders or different groups of surgery recommended. The sign of significant coefficients showed that decreasing the VAS associated with increasing HRQOL. Subjects with more BMI had better response to traditional treatment according to their HRQOL trend. Estimated coefficients for different covariates indicated that the variation of VAS was more effective than that of other considered factors (BMI and sex).

DISCUSSION

LBP and its related disabilities are major public health problems worldwide. The conventional treatment of LBP consists of medication, tissue stimulation (e.g., electrical stimulation, ultrasound), rest and orthotics.[31] Failure of the non-surgical treatment leads to alternative options, such as a variety of surgical approaches to achieve spinal fusion with various results.[32]

Given the inadequate results of traditional treatment and their side effects, there has been increasing usage of complementary and alternative medicine (CAM) by LBP sufferers to relieve their symptoms.[33]

There are more than 50 potential therapies promising to alleviate the pain, and provide a cure for this problem.[34] So, several groups of health care providers, such as physicians, physiotherapists, chiropractors, and a host of more "alternative" caregivers are involved in management of LBP. Some experts take this over-abundance of therapeutic options as a sign that "nothing works very well" singly for LBP[35] and recommend multi-disciplinary treatment programs.[36]

The results of the current study showed that our integrative treatment package comprised of herbal medicines, acupuncture, bee venom acupuncture, and a Korean massage (Chuna) significantly decreased VAS and ODI and improved the HRQOL of patients.

Several traditional Chinese and Korean herbal medicine including *Cibotium barometz, Atractylodes japonica*, *Ostericumkoreanum, Eucommia ulmoides, Acanthopanax Sessiliflorus, Achyranthesbidentata, Psoraleacorylifolia, Peucedanum japonicum, Lycium chinense, Boschniakia rossica*, and *Cuscuta chinensis* have been used as treatments for LBP in this study. The above herbal medicines in powder and decoction forms are part of the historically developed treatment practiced at Jaseng Hospital for low back pain.[21] It has been shown that the compounds of Cibotium barometz and Atractylodes japonica showed inhibition of osteoclast, and protection of the osteoblasts respectively. Furthermore, it has been reported that Eucommia ulmoides, Dioscorea spongiosa and Cuscuta chinensis have anti-osteoporotic effects through osteoblast-like cell proliferation, osteoclast inhibition effects[37] and recover bone mineral density.[38,39]

Psoralea corylifolia and Lycium chinense[40] have known anti-inflammatory effects[41] while Peucedanum japonicum and Boschniakia rossica are good anti-oxidant.[42,43]

Acupuncture is based on ancient Chinese philosophical theories about the flow of vital energy through the body along the discrete pathways termed meridians. In acupuncture, specific points alongside of the meridians are utilized to balance the energy flows within the body. Many different styles of acupuncture and adjunctive techniques have been developed and disseminated into other cultures.[44]

There are several systematic reviews on efficacy of acupuncture in LBP patients comparing acupuncture with sham acupuncture, other sham treatments, no additional treatment, or another active treatment. Acupuncture effectively relieves chronic LBP. No evidence suggests that acupuncture is more effective than other active therapies.[45]

Traditional Korean doctors have used apitoxin, or honey bee venom, as a type of pharmacopuncture. Bee venom is extracted from a honey bee by using electrical stimulation. It has been shown that Bee venom administration is effective in pain relief of rheumatoid and degenerative arthritis, which require long-term treatment, as well as resolution of inflammation.[46]

Several mechanisms have been suggested to clarify the bee venom induced antinociceptive and

anti-inflammatory effects, including the activation of spinal alpha 2-adrenoceptors of descending noradrenergic, adrenergic, and serotonergic pathways and activation of capsaicin-sensitive primary afferent (CSPA) fibers.[47-49]

The analgesic effects induced by BV acupuncture also may be attributable to bioactive BV compounds, including peptides (melittin, adolapin, apamin, and the mast-cell degranulating peptide), enzymes (phospholipase A2), and amines (histamine and epinephrine)[50]

Massage is a simple way of pain relief, which stimulates large diameter nerve fibers that finally inhibits nociceptive fibers. It may also provide its benefits through shifting the autonomic nervous system from a state of sympathetic response to a state of para-sympathetic response, and increasing the pain threshold through the release of endorphins[34]

The results of a systematic review showed that massage is beneficial for patients with sub-acute and chronic nonspecific LBP in terms of improving symptoms and function. Two studies compared massage to sham treatment reported that massage was superior for pain and function on both short and long-term follow-ups. However, a latest Cochrane review of spinal manipulation in chronic LBP concluded that spinal manipulative therapy results in a small, statistically significant but not clinically significant pain relieve and function in patients with chronic LBP compared with other treatments.[51]

To the best of our knowledge, this is the first study investigating the effect of an integrative treatment package on LBP. Furthermore, while most of the studies considered short term beneficial effects of traditional and CAM approach to relieve pain, the long observational period of 6 months allowed us to predict progress of treatment outcomes. However, we were unable to compare the results of our study to others and could not find which treatment of the package is more effective than others.

Our new analysis showed that the older participants in our study benefited more from the LBP integrated package. It means that the more age led to higher HRQOL with less VAS. The prevalence of benign back pain appears to increase with an increasing age, with a peak in the sixth decade. Back pain is one the four most commonly reported symptoms in the elderly[52] and the prevalence of osteoarthritis, disc degeneration, osteoporosis and spinal stenosis are known to increase with age.[53,54] Furthermore, it has been shown that the risk of disabling back pain rises in older age.[55] In light of this, it is highly desirable to find a safe way for LBP in elderly patients. Since, LBP has such human and financial impacts on society and since the numbers of people aged are increasing our package will be a good suggestion for this group.

Another new finding of the current study was the more benefits of the integrated package in patients with higher BMI. The data for association between obesity and low back pain appears to be controversial[56] however, there are stronger evidences showing that overweight and obesity are associated with an increased risk of low back pain.[57] Yet, there is no appropriate therapeutic approach for the obese patient with low back pain. So the more positive result of the integrated package for more obese patients in the current study is favorable.

One more interesting finding of the re-analysis of the results with new method is the similar results in patients with and without the herniated disc surgery. It seems that this package may lead to impressive outcomes even in patient with serious underlying patho-physiology similar other study.[58]

CONCLUSION

Our results suggest that multi-modal treatments may improve LBP by several mechanisms. We suggest a stepwise controlled study to address: (1) whether this package approach is more effective than other treatments; and (2) which treatment components of the package are more substantial than others. In summary, this integrative package was effective in the treatment of LBP with leg pain and warrants further rigorous investigations.

REFERENCES

1. Andersson GB. Epidemiological features of chronic low-back pain. Lancet 1999;354:581-5.
2. Anema JR, van der Beek AJ. Medically certified sickness absence. BMJ 2008;337:825-6.
3. Frymoyer JW. Back pain and sciatica. N Engl J Med 1988;318:291-300.
4. Allan DB, Waddell G. An historical perspective on low back pain and disability. Acta Orthop Scand Suppl 1989;234:1-23.

5. Papageorgiou AC, Croft PR, Thomas E, Ferry S, Jayson MI, Silman AJ. Influence of previous pain experience on the episode incidence of low back pain: Results from the South Manchester Back Pain Study. Pain 1996;66:181-5.
6. Spitzer WO, Leblanc FE, Dupuis M. Scientific approach to the assessment and management of activity-related spinal disorders. Spine 1987;12:S4-59.
7. Schmidt-Olsen S, Jorgensen U, Kaalund S, Sørensen J. Injuries among young soccer players. Am J Sports Med 1991;19:273-5.
8. Kujala UM, Salminen JJ, Taimela S, Oksanen A, Jaakkola L. Subject characteristics and low back pain in young athletes and nonathletes. Med Sci Sports Exerc 1992;24:627-32.
9. Deyo RA, Andersson G, Bombardier C, Cherkin DC, Keller RB, Lee CK, *et al*. Outcome measures for studying patients with low back pain. Spine 1994;19(Suppl 18):2032S-6.
10. Deyo RA, Battie M, Beurskens AJ, Bombardier C, Croft P, Koes B, *et al*. Outcome measures for low back pain research: A proposal for standardized use. Spine 1998;23:2003-13.
11. Testa MA, Simonson DC. Assesment of quality-of-life outcomes. N Engl J Med 1996;334:835-40.
12. Rumsfeld JS, MaWhinney S, McCarthy M Jr, Shroyer AL, VillaNueva CB, O'Brien M, *et al*. Health-related quality of life as a predictor of mortality following coronary artery bypass graft surgery. JAMA 1999;281:1298-303.
13. Krishnaney AA, Park A, Benzell EC. Surgical management of neck and LBP. Neurol Clin 2007;25:507-22.
14. Lin XJ, Chen CY. Advances on study of treatment of lumbar disk herniation by Chinese medicinal herbs. Zhongguo Zhong Yao Za Zhi 2007;32:186-91.
15. Bronfort GB, Haas M, Evans R, Kawchuk G, Dagenais S. Evidence-informed management of chronic LBP with spinal manipulation and mobilization. Spine J 2008;8:215-25.
16. Assendelft WJ, Morton SC, Ju EI, Suttorp MJ, Shekelle PG. Spinal manipulative therapy for LBP: A meta-analysis of effectiveness relative to other therapies. Ann Int Med 2003;138:E871-900.
17. Lee MS, Pitler MH, Shin BC, Kong JC, Ernst E. Bee venom acupuncture for musculoskeletal pain: a review. J Pain 2008;9:289-97.
18. Yuan J, Purepong N, Kerr DP, Park J, Bradbury I, McDonough S. Effectiveness of acupuncture for LBP. Spine 2008;33:E887-900.
19. Ammendolia C, Furlan AD, Imamura M, Irvin E, van Tulder M. Evidence-informed management of chronic LBP with needle acupuncture. Spine J 2008;8:160-72.
20. Cuong NX, Minh CV, Kiem PV, Huong HT, Ban NK, Nhiem NX, *et al*. Inhibitors of osteoclast formation from rhizomes of Cibotiumbarometz. J Nat Prod 2009;72:1673-7.
21. Park JJ, Shin J, Choi Y, Youn Y, Lee S, Kwon SR, *et al*. Integrative package for low back pain with leg pain in Korea: A prospective cohort study. Complement Therap Med 2010;18:78-86.
22. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: A comparison of six methods. Pain 1986;27:117-26.
23. Beurskens AJHM, de Vet HCW, Koke AJ. Responsiveness of functional status in LBP: comparison of different instruments. Pain 1996;95:71-6.
24. WareJr JE, Sherbourne D. The MOS 36-item short form health survey (SF-36). I: conceptual framework and item selection. Med Care 1992;30:473-83.
25. McHorney CA, Ware Jr JE, Lu JF, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). III: Tests of data quality, scaling assumptions, and reliability across diverse patient groups. Med Care 1994;32:40-66.
26. Sahu SK, Dey DK, Branco MD. A new class of multivariate skew distributions with applications to Bayesian regression models. Can J Stat 2003;31:129-50.
27. Azzalini A, Capitanio A. Statistical applications of the multivariate skew normal distributions. J R Stat Soc Series B , Series B 1999;61:579-602.
28. Azzalini A, Dal Cappello T, Kotz S. Log-skew-normal and log-skew-t distributions as models for family income data. J Income Distrib 2002;65:367-89.
29. Capitanio A, Azzalini A, Stanghellini E. Graphical models for skew-normal variates. Scandinavian J Stat 2003;30:129-44.
30. Sahu SK, Dey DK. On a Bayesian multivariate survival models with a skewed frailty. In Skew-Elliptical Distributions and their Applications: A Journey Beyond Normality. In: Genton MG, editor. London, Boca Raton, FL: CRC/Chapman and Hall; 2004. p. 321-38.
31. Cherkin DC, Deyo RA. Non-surgical hospitalization for low back pain. Is it necessary?. Spine 1993;18:1728-35.
32. Herkowitz HN, Sidhu KS. Lumbar Spine Fusion in the reatment of Degenerative Conditions: Current Indications and Recommendations. J Am Acad Orthop Surg 1995;3:123-35.
33. Ernst E, White A. The BBC survey of complementary medicine use in the UK. Complement Ther Med 2000;8:32-6.
34. Ernst E. Massage therapy for low back pain: A systematic review. J Pain Symptom Manage 1999;17:65-9.
35. Frank JW, Brooker AS, DeMaio SE, Kerr MS, Maetzel A, Shannon HS, *et al*. Disability resulting from occupational low back pain. Part II: What do we know about secondary prevention? A review of the scientific evidence on

prevention after disability begins. Spine (Phila Pa 1976) 1996;21:2918-29.
36. vanTulder M, Koes B. Low back pain and sciatica: Chronic. Clin Evid 2002;8:1171-87.
37. Yin J, Tezuka Y, Kouda K, Tran QL, Miyahara T, Chen Y, *et al*. Antiosteoporotic activity of the water extract of Dioscoreaspongiosa. Biol Pharm Bull 2004;27:583-6.
38. Yang L, Chen Q, Wang F, Zhang G. Antiosteoporotic compounds from seeds of Cuscutachinensis. J Ethnopharmacol 2011;135:553-60.
39. Yang HM, Shin HK, Kang YH, Kim JK. Cuscutachinensis extract promotes osteoblast differentiation and mineralization in human osteoblast-like MG-63 cells. J Med Food 2009;12:85-92.
40. Yamada P, Nemoto M, Shigemori H, Yokota S, Isoda H. Isolation of 5-(hydroxymethyl) furfural from Lyciumchinense and its inhibitory effect on the chemical mediator release by basophilic cells. Planta Med 2011;77:434-40.
41. Lee SW, Yun BR, Kim MH, Park CS, Lee WS, Oh HM, *et al*. Phenolic compounds isolated from Psoraleacorylifolia inhibit IL-6-induced STAT3 activation. Planta Med 2012;78:903-6.
42. Hisamoto M, Kikuzaki H, Ohigashi H, Nakatani N. Antioxidant compounds from the leaves of Peucedanumjaponicumthunb. J Agric Food Chem 2003;51:5255-61.
43. Manheimer E, White A, Berman B, Forys K, Ernst E. Meta-analysis: Acupuncture for low back pain. Ann Intern Med 2005;142:651-63.
44. Furlan AD, van Tulder M, Cherkin D, Tsukayama H, Lao L, Koes B, *et al*. Acupuncture and dry-needling for low back pain: An updated systematic review within the framework of the Cochrane collaboration. Spine (Phila Pa 1976) 2005;30:944-63.
45. Cherkin DC, Sherman KJ, Deyo RA, Shekelle PG. A review of the evidence for the effectiveness, safety, and cost of acupuncture, massage therapy, and spinal manipulation for back pain. Ann Intern Med 2003;138:898-906.
46. Chen HS, Qu F, He X, Liao D, Kang SM, Lu SJ. The anti-nociceptive effect and the possible mechanism of acupoint stimulation caused by chemical irritants in the bee venom pain model. Brain Res 2010;1355:61-9.
47. Kwon YB, Lee HJ, Han HJ, Mar WC, Kang SK, Yoon OB, *et al*. The water soluble fraction of bee venom produces antinociceptive and anti-nflammatory effects on rheumatoid arthritis in rats. Life Sci 2002;71:191-204.
48. Kwon YB, Lee JD, Lee HJ, Han HJ, Mar WC, Kang SK, *et al*. Bee venom injection into an acupuncture point reduces arthritis associated edema and nociceptive responses. Pain 2001;90:271-80.
49. Roh DH, Kim HW, Yoon SY, Kang SY, Kwon YB, Cho KH, *et al*. Bee venom injection significantly reduces nociceptive behavior in the mouse formalin test via capsaicin insensitive afferents. J Pain 2006;7:500-12.
50. Son DJ, Lee JW, Lee YH, Song HS, Lee CK, Hong JT. Therapeutic application of anti-arthritis, pain-releasing, and anti-cancer effects of bee venom and its constituent compounds. Pharmacol Ther 2007;115:246-70.
51. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain. Cochrane Database Syst Rev 2011;(2):CD008112.
52. Hoy D, Bain C, Williams G, March L, Brooks P, Blyth F, *et al*. A systematic review of the global prevalence of low back pain. Arthritis Rheum 2012;64:2028-37.
53. Dionne CE, Dunn KM, Croft PR. Does back pain prevalence really decrease with increasing age? A systematic review. Age Ageing 2006;35:229-34.
54. Docking RE, Fleming J, Brayne C, Zhao J, Macfarlane GJ, Jones GT; Cambridge City over-75s Cohort Study collaboration. Epidemiology of back pain in older adults: Prevalence and risk factors for back pain onset. Rheumatology (Oxford) 2011;50:1645-53.
55. Mirtz TA, Greene L. Is obesity a risk factor for low back pain? An example of using the evidence to answer a clinical question. Chiropr Osteopat 2005;13:2.
56. Shiri R, Karppinen J, Leino-Arjas P, Solovieva S, Viikari-Juntura E. The association between obesity and low back pain: A meta-analysis. Am J Epidemiol 2010;171:135-54.
57. Ibrahim T, Tleyjeh IM, Gabbar O. Surgical versus non-surgical treatment ofchronic low back pain: A meta-analysis of randomised trials. Int Orthop 2008;32:107-13.
58. Ibrahim T, Tleyjeh IM, Gabbar O. Surgical versus non-surgical treatment ofchronic low back pain: A meta-analysis of randomised trials. Int Orthop 2008;32:107-13.

Source of Support: Nil, **Conflict of Interest:** None declared.