Current Pain and Headache Reports (2019) 23: 86
https://doi.org/10.1007/s11916-019-0821-x

OTHER PAIN (N VADIVELU AND AD KAYE, SECTION EDITORS)

Treatment of Discogenic Low Back Pain: Current Treatment Strategies and Future Options—a Literature Review

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Published online: 9 November 2019

Abstract

Purpose of Review Many studies have demonstrated that discogenic low back pain is the most common type of chronic low back pain (CLBP), one of the major causes of disability, and has a major socioeconomic impact. Our aim is to review present therapeutic interventions for discogenic low back pain.

Recent Findings There are a multitude of treatments used in clinical practice to treat CLBP, but there is continued debate and lack of consensus among clinicians and the policy makers as to which modality is the best approach. Based on controlled evaluations, lumbar intervertebral discs have been shown to be the source of chronic back pain without disc herniation in 26 to 39% of patients. Treatment modalities include noninvasive treatments such as drug therapy, multiple physical modalities, and multidisciplinary biopsychosocial rehabilitation; interventional modalities such as intradiscal therapies and epidural injections; and regenerative modalities with disc injections of various solutions; and, finally, surgical approaches such as fusion and artificial disc replacement, all of which are accompanied by significant discussion, limited evidence, and lack of consensus.

Summary The results of this evaluation show that the evidence for drug therapy in chronic discogenic low back pain is limited; for multidisciplinary biopsychosocial rehabilitation, it is moderate; and for multiple physical and behavioral therapies, the evidence is limited. For intradiscal therapies, it is poor; for epidural injections, it is moderate; and for regenerative therapies, evidence levels of 3 to 4. The evidence for surgical fusions and disc replacement is similar, without superiority when compared with multidisciplinary biopsychosocial rehabilitation, well-designed physical therapy, or epidural injections.

Keywords Intervertebral disc · Degeneration · Diagnosis · Treatment · Discogenic low back pain

Introduction

Chronic low back pain (CLBP) is one of the most significant medical and social problems in the world today [1–4, 5•, 6•, 7•]. Dieleman et al. [3] showed that among the conditions with highest spending levels from 1966 to 2013, low back and neck pain were at the top, followed by diabetes. They also showed that in 2013, low back and neck pain accounted for the third highest amount. The estimated health care spending of $87.6 billion, with overall musculoskeletal disorders spending of $183.5 billion. Thus, determination of an appropriate strategy for managing CLBP and the disability related to it is crucial. Options range from simple exercise instructions to complex fusions [5•, 6•, 7•, 8, 9•, 10–15].

Lumbar degenerative disc disease without disc herniation, also known as discogenic pain, continues to be a difficult diagnosis with limited evidence and continued discussions that lack of consensus. The most commonly utilized modalities by interventional pain physicians, apart from structured exercise programs, comprehensive treatment modalities, epidural injections, and opioids are all associated with substantial debate and controversy [11–20]. Opioids have been associated with a significant number of deaths, even though the majority of them are related to illicit opioids, whereas epidural

This article is part of the Topical Collection on *Other Pain*

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injections and interventional techniques face criticism for lack of proof of effectiveness which has led to a reversal of growth patterns and a decline in some modalities of interventions [16–26]. However, the discussions and debate continue in reference to evidence in managing not only discogenic pain but also all types of low back pain and other painful conditions, including vertebral compression fractures, despite numerous publications showing variable evidence, with discordant conclusions [27•, 28–32, 33•, 34–56].

Discogenic low back pain does not involve low back pain caused by lumbar disc herniation; however, it does refer to low back pain mediated or modulated by changes in the internal structure of the lumbar intervertebral disc [5•, 9•, 57–60]. Discogenic pain originates from the development of fissures in the annulus fibrosus with consequent vascularization of growing granulation tissue and growth of nociceptive nerve fibers along the tear area [58]. With age, the intervertebral disc undergoes significant changes, including loss of water content from the nucleus pulposus, disc thinning, decreased levels of hyaluronic acid, keratinized sulfate, with increase in low molecular weight glycoprotein, fibril degeneration, and collagen fiber deposition. These changes lead to loss of elasticity of the nucleus pulposus, disc structure relaxation, cartilage cystic change, and fibrous ring cracks.

The intervertebral disc is the largest structure without blood supply in the body. The nucleus pulposus tissue is wrapped by the annulus and isolated from the peripheral blood circulation. Studies have found that degeneration of the intervertebral disc tissue reveals a high concentration of a variety of cytokines. When the annulus fibrosus ruptures, the nucleus pulposus is identified by the autoimmune system after exposure, which induces an autoimmune reaction and produces pro-inflammatory substances, including interleukin and tumor necrosis factor. Among them, interleukin-1 (IL-1) can stimulate prostaglandin E2 (prostaglandin, E2, PGE2) and 5-serotonin (5-hydroxytryptamine, 5-HT) synthesis and can increase the body's sensitivity to pain. Interleukin-6 (IL-6) can stimulate local inflammatory cell aggregation, activation, and inflammatory mediator release [5•, 57–60].

After the degeneration of the intervertebral disc, in the process of repairing the annulus fibrosus, granulation tissue and nerve endings of nerve walls can grow into the annulus fibrosus or even the nucleus pulposus. The nerve endings that extend into the annulus are unmyelinated nerve fibers, susceptible to stromal changes, inflammatory mediators of the stimulus, and pain information along the nerve sensory terminals. Damaged spinal nerve root pain signals can increase muscle stretch reflex activity, while inflammation-induced pain substances on the nerve stimulation can increase the stretch reflex of this muscle, which induces low back muscle spastic pain [58].

Diagnosis

Magnetic resonance imaging (MRI) usually demonstrates degeneration of the disc, the so-called black disc syndrome. MRI usually shows high signal area behind the annulus fibrosus, which has an important diagnostic value. It usually indicates annulus fibrosus rupture, histologically representing vascularized granulation tissue. The diagnostic criteria for internal disc disruption (IDD) established by the International Association for the Study of Pain include emergence of a concordant pain response during discography, internal annular disruption demonstrated by computed tomography after discography and at least one adjacent disc without concordant pain [5•, 8, 60]. The term discogenic low back pain, which is currently used in the literature, is in fact a specific IDD-induced low back pain. At present, IDD has been described as a distinct clinical entity to be distinguished from other painful processes, such as degenerative disc disease and segmental instability [5•]. In one study, according to discography, Peng et al. [59] classified discogenic low back pain into 2 types which are supported clinically and with theoretical evidence, including annular disruption-induced low back pain and internal endplate disruption-induced low back pain.

Clinically, these 2 types of low back pain should be confirmed by lumbar discography. Painful intervertebral discs during contrast injection indicate that the contrast agent leaks through the radial annulus either to the disc or to the vertebral body through the radial endplate, both of which induce the patient's usual low back pain response. Theoretically, any lumbar vertebra that receives innervation and its adjacent soft tissue structure may be the origin of low back pain [60]. Manchikanti et al. [5•], in an update of the systematic appraisal of the accuracy and utility of discography in chronic spinal pain, showed variable prevalence of 16.9 to 26% for discogenic pain and 16.9 to 42% for internal disc disruption. They utilized 5 diagnostic assessment studies evaluating prevalence of discogenic pain in CLBP without disc herniation [61–65]. Manchikanti et al. [5•] provided level 2 evidence for lumbar provocation discography based on methodologic quality assessment criteria. Significant controversy was raised by Carragee et al. in reference to false-positive rates of discography [66]. Wolfer et al. [66] performed a systematic review in 2009 addressing issues related to Carragee's criticism. After reviewing all the studies, Wolfer et al. addressed this issue and performed a systematic review and meta-analysis of lumbar provocation discography in asymptomatic participants, with identification of 11 studies meeting inclusion criteria, yielding contradictory results to the opinions of Carragee et al. Wolfer et al. [66] analyzed chronic pain patients without low back pain and showed that the false-positive rate was 5.6% per patient and 3.85% per disc. Thus, Wolfer et al. [66] concluded chronic pain does not appear to be a confounding factor and patients with chronic pain possess

the ability to distinguish between pathologic and nonpathologic discs, namely positive and negative discs. They also extensively analyzed other groups including those with iliac crest pain after bone grafting, chronic neck pain, somatization disorder, and post discectomy. Overall, they showed low false-positive rates in patients with iliac crest pain after bone grafting of 12% and 7.1%, whereas false-positive rate in patients with chronic neck pain was 0% compared to post discectomy patients, 15% and 9.1% either per patient or per disc. Overall, the meta-analysis led Wolfer et al. [66] to recommend a more stringent, low pressure, positive criteria, since it was associated with a low false-positive rate.

Treatment

Natural History

The natural course of discogenic low back pain is of great clinical significance in the development of a treatment plan for discogenic low back pain. A prospective clinical study during a 4-year follow-up period indicated that the natural history of discogenic low back pain was chronic but persistent; 68.8% of patients had no change in pain and disability, as in the original case. This result indicates that most of the patients underwent a longer period of low back pain, and the original did not change significantly [67].

Drug Therapy

Multiple challenges persist in managing discogenic pain with drug therapy including balancing the effectiveness and adverse effects of each class of drugs. Multiple systematic reviews assessing the value and effectiveness of pharmacologic management of CLBP with various drugs showed that nonsteroidal antiinflammatory drugs (NSAIDs) [16–20] and opioids [16, 17, 68–71] are the most commonly utilized drugs in managing CLBP. Recommendations derived from these systematic reviews not only include consideration of NSAIDs as a treatment for CLBP with favorable effectiveness but also associated with significant adverse effects. It has been estimated that approximately 60 million Americans regularly use NSAIDs on a chronic basis, but with significant gastrointestinal complications in up to 2% of the users, and with a reported 120,000 hospital admissions and over 17,000 deaths per year [72]. Among these drugs, acetaminophen has fair evidence for pain relief but has been reported to be responsible for almost 1000 deaths in the USA alone [72].

Effectiveness of muscle relaxants has not been well studied [68–71]. In addition, antidepressant therapy has been assessed in multiple systematic reviews [68–71]. However, the results of the systematic review showed lack of effectiveness of antidepressants, even though they have been shown to be effective in various types of CLBP. Further, patients with associated depression may benefit from antidepressant therapy providing analgesia in addition to antidepressant effects. Effectiveness and role of antiepileptic drugs also have been studied. However, their role is well defined for widespread pain with highly variable effectiveness in only a small proportion of patients with low back pain [71, 73]. Benzodiazepines have been used in CLBP; however, multiple issues related to benzodiazepines have curtailed such uses and the use of benzodiazepines is limited to anxiety and the combination with opioids may result in multiple adverse consequences [74, 75].

Systematic corticosteroids have been studied mostly for radicular pain rather than CLBP with lack of proven effectiveness. Opioids are the most commonly used drugs in CLBP; however, their use has encountered extensive controversy and criticism with multiple adverse consequences contributing to the current opioid epidemic [16, 17, 19, 20]. Thus, low-dose opioids may be recommended in highly select patients, when not only pain relief, but increased functional status is demonstrated without development of tolerance, dependency, and other side effects. In addition to the traditional drugs, multiple herbal drugs also have been used [8].

Physical and Rehabilitation Therapy

Multiple interventions related to structured exercise program and physical therapy and rehabilitation modalities have been utilized in managing chronic discogenic pain. Many of these modalities are utilized by multiple disciplines and often in conjunction with drug therapy, interventional modalities, and surgery. A systematic review of various physical modalities in rehabilitation [76] showed that the only modality with significant effectiveness was multidisciplinary biopsychosocial rehabilitation. They showed lack of significant evidence for the effectiveness of exercise therapy, back schools, education, massage, behavioral treatment, transcutaneous electrical nerve stimulation (TENS), traction, and low-level laser therapy.

However, another systematic review by the same authors [77] showed improved pain intensity and disability with an improvement in long-term function compared with usual care with exercise therapy. A systematic review of back schools for nonspecific low back pain [78], with inclusion of 19 randomized controlled trials (RCTs), showed moderate evidence, suggesting that back schools, in an occupational setting, improved function with reduction in pain and also showed improved return to work status. Others also have showed that massage was significantly better than physical therapy at improving back pain and disability, even though it was associated with higher costs [79]. Traction, manipulation, massage, and acupuncture yielded overall mixed results [11, 78–80].

Overall, multidisciplinary biopsychosocial rehabilitation appears to be the favorite and recommended treatment among researchers, even though in practice, this has not been used

frequently. The literature shows discordant results in reference to the effects of biopsychosocial rehabilitation; however, there is more evidence in favor of multidisciplinary biopsychosocial rehabilitation [76, 81].

In practical terms, education, structured exercise therapy, and behavioral management have been recommended due to their noninvasiveness, low cost, and effectiveness in conjunction with other treatments.

Interventional Therapies

Epidural Injections

Multiple publications have indicated the effectiveness and cost utility of epidural injections in axial low back pain, which is considered as discogenic low back pain after eliminating pain secondary to facet joints and sacroiliac joints and also without evidence of disc herniation. Systematic reviews assessing the effectiveness of epidural injections in managing low back and lower extremity pain in various conditions have shown significant effectiveness based on RCTs for axial low back pain [7•, 28, 46, 82–84]. Cost utility was similar to disc herniation, central spinal stenosis, and post surgery syndrome [48, 85]. Further, it was also shown that lumbar interlaminar epidural injection was superior to caudal epidural injections and the effectiveness in discogenic pain was similar to disc herniation and superior to central spinal stenosis and post surgery syndrome [7•, 84]. Epidural injections were also shown to be superior to fusion and disc arthroplasty [6•]. Manchikanti et al. [82, 83] studied the role of epidural injections with or without steroids in 2 RCTs with either an interlaminar approach or a caudal approach in discogenic pain without disc herniation after exclusion of facet joint and sacroiliac joint pain. Overall, caudal epidural or interlaminar epidural approach showed significant improvement in pain and function (50% improvement of pain and functional status). They also separated the patients into responsive and nonresponsive groups. The patients who were responsive with at least 3 weeks of relief with the first 2 procedures fared better than overall when all patients were considered. Consequently, significant improvement was observed in both approaches with 72% showing significant improvement in the nonresponsive group and 80% showing significant improvement in the responsive group of patients receiving local anesthetic only, whereas the response was 67% in the nonresponsive group and 70% in the responsive group of patients receiving local anesthetic with steroids at the end of the 2 years in the lumbar interlaminar epidural injection group. In the caudal group, however, significant improvement was observed in 54% in nonresponsive group, 84% in the responsive group with local anesthetic only, whereas it was 60% or 73% in the nonresponsive and responsive groups respectively of the patients in the local anesthetic and steroid groups at 24 months. Overall, there was no significant difference whether steroids were added or not. All patients received intermittent injections with the return of the pain and decrease in functional status, with total procedures of 6 over a period of 2 years on average. Overall, superiority was demonstrated for interlaminar approaches. Further, cost utility analysis showed a cost of $3628 per quality-adjusted life year (QALY) improvement with caudal epidural injections [85], whereas it was $3303 per QALY with interlaminar epidural injections [46].

Percutaneous Intradiscal Therapies

Percutaneous intradiscal therapies are administered to alter the internal mechanics of the disc or the nerve supply either by application of heat, radiofrequency, or injection of various chemicals into the disc. These modalities include intradiscal electrothermal annuloplasty (IDEA), biacuplasty, intradiscal radiofrequency, and injections of intradiscal methylene blue or other chemicals. Intradiscal procedures applying heat have been collectively termed as "thermal annular procedures" [9•], and the Centers for Medicare & Medicaid Services (CMS) has described these procedures as thermal intradiscal procedures with issuance of a noncoverage policy due to lack of evidence for all thermal intradiscal procedures.

The intradiscal electrothermal therapy (IDET) was the first modality introduced with heat therapy, with extensive literature, but only 2 RCTs [86, 87]. Pauza et al. [86] in an RCT with publication of 6 month results showed significant improvement with pain and function compared to sham therapy. These results have been considered to show lack of efficacy due to its modest effect with 56% of the IDET group improving by more than 2 Visual Analog Scale (VAS) scores, whereas 38% of the control group also improved. Thus, the proportion of patients in the treated group improving with 50% improvement was only 40%, whereas it was 33% of the control group. The second RCT [87] showed no significant benefits for IDET over sham therapy. Both studies were criticized by opponents and proponents of the studies.

The transdiscal radiofrequency or biacuplasty utilizing 2 radiofrequency probes inserted into an affected intervertebral disc also has been studied. The proposed mechanism of action for intradiscal biacuplasty is the coagulation of the nociceptors within the posterior aspect of the disc [9•]. In a single placebo–controlled RCT [88], the results showed significant improvement in pain, functional status, and disability in the intradiscal biacuplasty group at 6 months compared with patients who received sham treatment. The trial has been criticized for its limitations. In addition, percutaneous intradiscal radiofrequency thermocoagulation using radiofrequency current was also studied with heating of the intervertebral disc in 2 RCTs comparing it with sham control [89, 90].

Helm et al. [9•] in an assessment of thermal annular procedures in treating discogenic pain, in a systematic review, with inclusion of 49 studies with only 4 RCTs concluded that there was strong evidence of efficacy of biacuplasty in the treatment of chronic refractory discogenic pain. They also showed level III or moderate evidence in support of IDET, and there was no evidence supporting the Disctrode. Consequently, it was given a level V evidence status, which is also considered as limited. Further, recently, Guo et al. [91] performed a meta-analysis of intradiscal methylene blue injection for discogenic low back pain with inclusion of 5 studies. They concluded that intradiscal methylene blue injection can reduce pain severity and improve the disability scores in individuals with discogenic low back pain. The results of the meta-analysis indicated that the effects of intradiscal methylene blue injection between preoperation and post operation on discogenic low back pain were significant based on 3 month pain scales and Oswestry Disability Index (ODI). A recent RCT [92] showed lack of effectiveness of intradiscal methylene blue injection.

Regenerative Medicine Therapies

Regenerative cell–based therapies have been proposed in recent years in the management of low back pain, specifically in discogenic pain, with injection of medicinal signaling cells or mesenchymal stem cells (MSCs) and platelet-rich plasma (PRP). There have been multiple systematic reviews published based on a few well conducted RCTs [10]. In a recent systematic review, Sanapati et al. [10] identified 12 studies with lumbar disc injections and 5 studies with epidural injections. Evidence based on a single-arm meta-analysis of RCTs and observational studies, disc injections of PRP and MSCs showed level III evidence, compared to epidural injections with a single RCT and other available studies showing level IV evidence.

Spinal Cord Stimulation

Dorsal or spinal cord stimulation (SCS) is a minimally invasive pain management option for refractory chronic pain. It has been shown that SCS is an efficacious, safe, and cost-effective alternative to treat CLBP, including the reduction of pain medications (including opiates), improving function and quality of life [93]. In a prospective observational study conducted in an urban pain management center, it was found that SCS may provide effective pain relief, improve disability, and reduce opioid usage in patients with discogenic pain as well [93].

Surgical Treatment

Interbody Fusion

Interbody fusion includes anterior lumbar interbody fusion, posterior lumbar interbody fusion, and/or transforaminal lumbar interbody fusion. In recent years, there has been development of extreme lateral interbody fusion [94]. In terms of instruments, the development of pedicle screw systems and intervertebral fusion devices has improved the success rate of intervertebral fusion. A recent randomized, prospective clinical study clearly revealed that lumbar fusion is superior to nonsurgical treatment for discogenic low back pain [95]. Guo et al. [96] conducted a clinical controlled study, also demonstrating that anterior discectomy with translaminar facet screws and posterior discectomy with pedicle screw fixation could effectively relieve pain more than radiofrequency. But surgical intervention should still be considered the last treatment of low back pain. At present, interbody fusion has become the gold standard in the treatment of discogenic low back pain, but clinical follow-up results suggest that there is still fusion failure, chronic pain, adjacent segment degeneration, and other late complications [97]. However, comparative analysis of evidence with fusion showed significant improvement with epidural injections compared to fusion.

Prosthesis Replacement

Prosthetic replacement uses artificial prostheses to restore the height of the intervertebral space as well as the disc biomechanical structure and load capacity. Benefits include segmental stability and segmental movement purposes. This technique restores not only the lumbar vertebrae natural "weight" bearing but also motor function. This technique completely removes intervertebral disc tissue, which eliminates inflammatory stimulation and autoimmune reaction, thus relieving pain symptoms. Discogenic low back pain is the best indication for prosthetic replacement. Prosthetic replacement includes prosthetic disc nucleus (PDN) and artificial disc replacement (ADR). At present, PDN products tend to be close to the biomechanics of the human nucleus pulposus. PDN use has a major limitation as it must require the integrity of the annulus to avoid prosthesis prolapse. ADR can maintain the physiological state of the activity of the vertebral body. Compared with interbody fusion, prosthesis replacement is a relatively new technology. Thavaneswaran et al. [98] have pointed out that in the short and medium terms, ADR and lumbar fusion safety and efficacy are similar. But, the scope of application of prosthetic replacement is significantly smaller than intervertebral fusion, and there is no sufficient evidence to prove that its long-term efficacy is better than intervertebral fusion. The spine surgical community should be, therefore, prudent to adopt this technology on a large scale,

despite the fact that total disc replacement seems to be effective in treating low back pain in selected patients and in the short term is at least equivalent to fusion surgery [99]. A prospective, multicenter, randomized, controlled clinical trial has revealed that a single-level active total disc replacement is safe and effective for the treatment of symptomatic lumbar degenerative disc disease at 2 years [100]. However, comparative analysis with epidural injections showed lack of effectiveness of prosthesis.

Dynamic Fixation System

Dynamic fixation systems are divided into nonfusion of dynamic fixation and fusion of dynamic fixation. Nonfusion of dynamic fixation refers to implant in fusion without bone graft to help spinal motion segment movement and change load transfer. The purpose is to change the way of motion segment carrying load and to control the abnormal activities between segments to maintain transfer of physiological load segment in order to achieve pain relief and prevention of adjacent segment degeneration. Fusion of dynamic fixation makes the lumbar vertebrae stable and promotes fusion of fixed segments, which can effectively disperse the internal fixed load conduction. A clinical trial has proved safe enough to be used in surgical patients affected by lumbar spine instability. Dynamic fixation system was able to provide significant improvements in disability and pain scores with a reasonable percentage of complications [101].

Conclusion

Treatment for chronic discogenic low back pain has traditionally been limited to either conservative management or invasive procedures including spinal fusion and recently spinal arthroplasty. If conservative treatment fails, then surgical fusion is commonly considered. However, the present evidence shows the effectiveness of epidural injections, intradiscal therapies, and intradiscal injections of PRP and MSCs. Additionally, biological therapy is at present the focus of research and theoretically may restore height and structure of the disc. Biological treatment methods include intervertebral disc growth factor injection, transgenic therapy, and cell injection therapy. Basic and clinical studies have found that intervertebral disc MSC transplantation may be a promising treatment.

Discogenic low back pain caused by dysfunction will be an increasingly serious public health problem. Intervertebral disc replacement needs development of new materials and structures to make it more consistent with biomechanical characteristics of the disc, while observing its long-term efficacy. The current focus of clinical and basic research is in used tissue engineering, which tries to carry out gene therapy and protein-based growth factor treatment, as well as clear stem cell transplantation after the phenotypic changes and the expression of cytokines and related genes. The results of the present investigation suggest that continuous development of biological technology might provide an important and significant role in the treatment of discogenic low back pain.

Compliance with Ethical Standards

Conflict of Interest Lei Zhao and Laxmaiah Manchikanti declare no conflict of interest. Dr. Kaye is a speaker for Merck. Dr. Abd-Elsayed is a consultant for Medtronic, StimWave, Avanos and Sollis.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. US Burden of Disease Collaborators. The state of US health, 1999–2010: burden of diseases, injuries, and risk factors. JAMA. 2013;310:591–608.
2. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, et al. The global burden of low back pain: estimates from the Global Burden of Disease 2010 study. Ann Rheum Dis. 2014;73:968–74.
3. Dieleman JL, Baral R, Birger M, Bui AL, Bulchis A, Chapin A, et al. US spending on personal health care and public health, 1996–2013. JAMA. 2016;316:2627–46.
4. Geurts JW, Willems PC, Kallewaard JW, van Kleef M, Dirksen C. The impact of chronic discogenic low back pain: costs and patients' burden. Pain Res Manag. 2018;2018:4696180.
5. • Manchikanti L, Soin A, Benyamin RM, Singh V, Falco FJ, Calodney AK, et al. An update of the systematic appraisal of the accuracy and utility of discography in chronic spinal pain. Pain Physician. 2018;21:91–110 **Important update on discography in chronic spinal pain**.
6. • Manchikanti L, Staats PS, Nampiaparampil DE, Hirsch JA. What is the role of epidural injections in the treatment of lumbar discogenic pain: a systematic review of comparative analysis with fusion and disc arthroplasty. Korean J Pain. 2015;28:75–87 **Important review on the role of epidurals in lumbar discogenic pain**.
7. • Manchikanti L, Pampati V, Benyamin RM, Boswell MV. Analysis of efficacy differences between caudal and lumbar interlaminar epidural injections in chronic lumbar axial discogenic pain: local anesthetic alone vs. local combined with steroids. Int J Med Sci. 2015;12:214–22 **Important analysis of efficacy between caudal and lumbar interlaminar injections in discogenic pain**.
8. Manchikanti L, Hirsch JA. An update on the management of chronic lumbar discogenic pain. Pain Manag. 2015;5:373–86.
9. • Helm S 2nd, Simopoulos TT, Stojanovic MP, Abdi S, El Terany MA. Effectiveness of thermal annular procedures in treating discogenic low back pain. Pain Physician. 2017;20:447–70 **Important review on thermal annular procedures for discogenic low back pain**.
10. Sanapati J, Manchikanti L, Atluri S, Jordan S, Albers SL, Pappolla MA, et al. Do regenerative medicine therapies provide long-term

relief in chronic low back pain: a systematic review and metaanalysis. Pain Physician. 2018;21:515–40.
11. Rubinstein SM, van Middelkoop M, Assendelft WJ, de Boer MR, van Tulder MW. Spinal manipulative therapy for chronic low-back pain: an update of a Cochrane review. Spine (Phila Pa 1976). 2011;36:E825–46.
12. Rajaee SS, Bae HW, Kanim LE, Delamarter RB. Spinal fusion in the United States: analysis of trends from 1998 to 2008. Spine (Phila Pa 1976). 2012;37:67–76.
13. Phillips FM, Slosar PJ, Youssef JA, Andersson G, Papatheofanis F. Lumbar spine fusion for chronic low back pain due to degenerative disc disease: a systematic review. Spine (Phila Pa 1976). 2013;38:E409–22.
14. Bydon M, De la Garza-Ramos R, Macki M, Baker A, Gokaslan AK, Bydon A. Lumbar fusion versus nonoperative management for treatment of discogenic low back pain: a systematic review and meta-analysis of randomized controlled trials. J Spinal Disord Tech. 2014;27:297–304.
15. Saltychev M, Eskola M, Laimi K. Lumbar fusion compared with conservative treatment in patients with chronic low back pain: a meta-analysis. Int J Rehabil Res. 2014;37:2–8.
16. Manchikanti L, Kaye AM, Knezevic NN, McAnally H, Trescot AM, Blank S, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician. 2017;20:S3–92.
17. Sanger N, Bhatt M, Singhal N, Ramsden K, Baptist-Mohseni N, Panesar B, et al. Adverse outcomes associated with prescription opioids for acute low back pain: a systematic review and meta-analysis. Pain Physician. 2019;22:119–38.
18. Navani A, Manchikanti L, Albers SL, Latchaw RE, Sanapati J, Kaye AD, et al. Responsible, safe, and effective use of biologics in the management of low back pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician. 2019;22:S1–S74.
19. Manchikanti L, Sanapati J, Benyamin RM, Atluri S, Kaye AD, Hirsch JA. Reframing the prevention strategies of the opioid crisis: focusing on prescription opioids, fentanyl, and heroin epidemic. Pain Physician. 2018;21:309–26.
20. Chakravarthy K, Manchikanti L, Kaye AD, Christo PJ. Reframing the role of neuromodulation therapy in the chronic pain treatment paradigm. Pain Physician. 2018;21:507–13.
21. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Reversal of growth of utilization of interventional techniques in managing chronic pain in Medicare population post Affordable Care Act. Pain Physician. 2017;20:551–67.
22. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampai V, Hirsch JA. Comparative analysis of utilization of epidural procedures in managing chronic pain in the Medicare population: pre and post Affordable Care Act. Spine (Phila Pa 1976). 2019;44:220–32.
23. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. Declining utilization of percutaneous epidural adhesiolysis in Medicare population: evidence-based or over-regulated? IPM Reports. 2018;2:9–18.
24. Manchikanti MV, Manchikanti L, Kaye AD, Pampati V, Hirsch JA. Usage patterns of sacroiliac joint injections – a comparative evaluation of pre and post Affordable Care Act in Medicare population. IPM Reports. 2018;2:157–66.
25. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. **Cost** calculation methodology exacerbates site-of-service differentials by 10- to 18-fold for soft tissue and joint injections in hospital outpatient departments. IPM Reports. 2017;1:183–9.
26. Manchikanti L, Singh V, Benyamin RM, Kaye AD, Pampati V, Hirsch JA. Reframing Medicare physician payment policy for 2019: a look at proposed policy. Pain Physician. 2018;21:415–32.
27.• Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural injections for lumbar radiculopathy and spinal stenosis: a comparative systematic review and meta-analysis. Pain Physician. 2016;19:E365–410 **Systematic review on epidural injections for spinal stenosis and lumbar radiculopathy**.
28. Manchikanti L, Nampiaparampil DE, Manchikanti KN, Falco FJE, Singh V, Benyamin RM, et al. Comparison of the efficacy of saline, local anesthetics, and steroids in epidural and facet joint injections for the management of spinal pain: a systematic review of randomized controlled trials. Surg Neurol Int. 2015;6:S194–235.
29. Manchikanti L, Kaye AD, Manchikanti KN, Boswell MV, Pampati V, Hirsch JA. Efficacy of epidural injections in the treatment of lumbar central spinal stenosis: a systematic review. Anesth Pain Med. 2015;5:e23139.
30. Chou R, Hashimoto R, Friedly J, Fu R, Bougatsos C, Dana T, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: a systematic review and meta-analysis. Ann Intern Med. 2015;163:373–81.
31. Lewis RA, Williams NH, Sutton AJ, Burton K, Din NU, Matar HE, et al. Comparative clinical effectiveness of management strategies for sciatica: systematic review and network meta-analyses. Spine J. 2015;15:1461–77.
32. Guo JR, Jin XJ, Shen HC, Wang H, Zhou X, Liu XQ, et al. A comparison of the efficacy and tolerability of the treatments for sciatica: a network meta-analysis. Ann Pharmacother. 2017;51:1041–52.
33.• Manchikanti L, Boswell MV, Kaye AD, Helm S II, Hirsch JA. Therapeutic role of placebo: evolution of a new paradigm in understanding research and clinical practice. Pain Physician. 2017;20:363–86 **Role of placebo in research and clinical practice**.
34. Lee JH, Kim DH, Kim DH, Shin KH, Park SJ, Lee GJ, et al. Comparison of clinical efficacy of epidural injection with or without steroid in lumbosacral disc herniation: a systematic review and meta-analysis. Pain Physician. 2018;21:449–68.
35. Lee JH, Shin KH, Park SJ, Lee GJ, Lee CH, Kim DH, et al. Comparison of clinical efficacy between transforaminal and interlaminar epidural injections in lumbosacral disc herniation: a systematic review and meta-analysis. Pain Physician. 2018;21:433–48.
36. Shen J, Xu S, Xu S, Ye S, Hao J. Fusion or not for degenerative lumbar spinal stenosis: a meta-analysis and systematic review. Pain Physician. 2018;21:1–8.
37. Song D, He A, Xu R, Xiu X, Wei Y. Efficacy of pain relief in different postherpetic neuralgia therapies: a network meta-analysis. Pain Physician. 2018;21:19–32.
38. Manchikanti L, Malla Y, Cash KA, Pampati V, Hirsch JA. Comparison of effectiveness for fluoroscopic cervical interlaminar epidural injections with or without steroid in cervical post-surgery syndrome. Korean J Pain. 2018;31:277–88.
39. Fu X, Tang L, Wang C, Li M, Wu H, Li J, et al. A network meta-analysis to compare the efficacy of steroid and antiviral medications for facial paralysis from Bell's palsy. Pain Physician. 2018;21:559–69.
40. Hou S, Huh B, Kim HK, Kim KH, Abdi S. Treatment of chemotherapy-induced peripheral neuropathy: systematic review and recommendations. Pain Physician. 2018;21:571–92.
41. Cho JH, Lee JH, Song KS, Hong JY, Joo YS, Lee DH, et al. Treatment outcomes for patients with failed back surgery. Pain Physician. 2017;20:E29–43.
42. Yeh SW, Hong CH, Shih MC, Tam KW, Huang YH. Low-level laser therapy for fibromyalgia: a systematic review and meta-analysis. Pain Physician. 2019;22:241–54.

43. Halpern MT, Fiero MH. Factors influencing receipt of interventional pain management among Medicaid beneficiaries with cancer. Pain Physician. 2019;22:E147–55.
44. Kaye AD, Manchikanti L, Novitch MB, Mungrue IN, Anwar M, Jones MR, et al. Responsible, safe, and effective use of antithrombotics and anticoagulants in patients undergoing interventional techniques: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician. 2019;22:S75–S128.
45. Zhiyong C, Yun T, Hui F, Zhongwei Y, Zhaorui L. Unilateral versus bilateral balloon kyphoplasty for osteoporotic vertebral compression fractures: a systematic review of overlapping meta-analyses. Pain Physician. 2019;22:15–28.
46. Kaye AD, Manchikanti L, Abdi S, Atluri S, Bakshi S, Benyamin R, et al. Efficacy of epidural injections in managing chronic spinal pain: a best evidence synthesis. Pain Physician. 2015;18:E939–E1004.
47. Wagemakers SH, van der Velden JM, Gerlich AS, Hindriks-Keegstra AW, van Dijk JFM, Verhoeff JJC. A systematic review of devices and techniques that objectively measure patients' pain. Pain Physician. 2019;22:1–13.
48. Vu Tran Z, Ivashchenko A, Brooks L. Sacroiliac joint fusion methodology - minimally invasive compared to screw-type surgeries: a systematic review and meta-analysis. Pain Physician. 2019;22:29–40.
49. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Therapeutic lumbar facet joint nerve blocks in the treatment of chronic low back pain: cost utility analysis based on a randomized controlled trial. Korean J Pain. 2018;31:27–38.
50. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Cost utility analysis of cervical therapeutic medial branch blocks in managing chronic neck pain. Int J Med Sci. 2017;14:1307–16.
51. Wu PF, Li YW, Wang B, Jiang B, Tu ZM, Lv GH. Posterior cervical foraminotomy via full-endoscopic versus microendoscopic approach for radiculopathy: a systematic review and meta-analysis. Pain Physician. 2019;22:41–52.
52. Clark W, Bird P, Gonski P, Diamond TH, Smerdely P, McNeil HP, et al. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2016;388:1408–16.
53. Xiang GH, Tong MJ, Lou C, Zhu SP, Guo WJ, Ke CR. The role of unilateral balloon kyphoplasty for the treatment of patients with OVCFS: a systematic review and meta-analysis. Pain Physician. 2018;21:209–18.
54. Chen X, Guo W, Li Q, Ou Z, Lao Z, Liu Y, et al. Is unilateral percutaneous kyphoplasty superior to bilateral percutaneous kyphoplasty for osteoporotic vertebral compression fractures? Evidence from a systematic review of discordant meta-analyses. Pain Physician. 2018;21:327–36.
55. Rosian K, Hawlik K, Piso B. Efficacy assessment of radiofrequency ablation as a palliative pain treatment in patients with painful metastatic spinal lesions: a systematic review. Pain Physician. 2018;21:E467–76.
56. Beall DP, Coe JD, McIlduff M, Bloch D, Hornberger J, Warner C, et al. Serious adverse events associated with readmission through one year after vertebral augmentation with either a polyetheretherketone implant or balloon kyphoplasty. Pain Physician. 2017;20:521–8.
57. Capossela S, Schläfli P, Bertolo A, Janner T, Stadler BM, Pötzel T, et al. Degenerated human intervertebral discs contain autoantibodies against extracellular matrix proteins. Eur Cell Mater. 2014;27:251–63.
58. García-Cosamalón J, del Valle ME, Calavia MG, García-Suárez O, López-Muñiz A, Otero J, et al. Intervertebral disc, sensory nerves and neurotrophins: who is who in discogenic pain? J Anat. 2010;217:1–15.
59. Peng BG. Pathophysiology, diagnosis, and treatment of discogenic low back pain. World J Orthop. 2013;4:42–52.
60. Yang G, Liao W, Shen M, Mei H. Insight into neural mechanisms underlying discogenic back pain. J Int Med Res. 2018;46:4427–36.
61. Manchikanti L, Singh V, Pampati V, Damron K, Barnhill R, Beyer C, et al. Evaluation of the relative contributions of various structures in chronic low back pain. Pain Physician. 2001;4:308–16.
62. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine (Phila Pa 1976). 1995;20:1878–83.
63. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? Pain Med. 2011;12:224–33.
64. Bokov A, Perlmutter O, Aleynik A, Rasteryaeva M, Mlyavykh S. The potential impact of various diagnostic strategies in cases of chronic pain syndromes associated with lumbar spine degeneration. J Pain Res. 2013;6:289–96.
65. Verrills P, Nowesenitz G, Barnard A. Prevalence and characteristics of discogenic pain in tertiary practice: 223 consecutive cases utilizing lumbar discography. Pain Med. 2015;16:1490–9.
66. Wolfer L, Derby R, Lee JE, Lee SH. Systematic review of lumbar provocation discography in asymptomatic subjects with a meta-analysis of false-positive rates. Pain Physician. 2008;11:513–38.
67. Peng B, Fu X, Pang X, Li D, Liu W, Gao C, et al. Prospective clinical study on natural history of discogenic low back pain at 4 years of follow-up. Pain Physician. 2012;15:525–32.
68. Kuijpers T, van Middelkoop M, Rubinstein SM, Ostelo R, Verhagen A, Koes BW, et al. A systematic review on the effectiveness of pharmacological interventions for chronic non-specific low-back pain. Eur Spine J. 2011;20:40–50.
69. Chung JW, Zeng Y, Wong T. Drug therapy for the treatment of chronic nonspecific low back pain: systematic review and meta-analysis. Pain Physician. 2013;16:E685–704.
70. White AP, Arnold PM, Norvell DC, Ecker E, Fehlings MG. Pharmacologic management of chronic low back pain: synthesis of the evidence. Spine (Phila Pa 1976). 2011;36:S131–43.
71. Chou R, Huffman LH, American Pain Society; American College of Physicians. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. Ann Intern Med. 2007;147:505–14.
72. Leavitt SB. NSAID dangers may limit pain-relief options. Pain-Topics http://updates.pain-topics.org
73. Moore A, Wiffen P, Kalso E. Antiepileptic drugs for neuropathic pain and fibromyalgia. JAMA. 2014;312:182–3.
74. Deyo RA, Von Korff M, Duhrkoop D. Opioids for low back pain. BMJ. 2015;350:g6380.
75. Manchikanti L, Manchikanti KN, Kaye AD, Kaye AM, Hirsch JA. Challenges and concerns of persistent opioid use in cancer patients. Expert Rev Anticancer Ther. 2018;18:705–18.
76. van Middelkoop M, Rubinstein SM, Kuijpers T, Verhagen AP, Ostelo R, Koes BW, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. Eur Spine J. 2011;20:19–39.
77. van Middelkoop M, Rubinstein SM, Verhagen AP, Ostelo RW, Koes BW, van Tulder MW. Exercise therapy for chronic nonspecific low-back pain. Best Pract Res Clin Rheumatol. 2010;24:193–204.
78. Heymans MW, van Tulder MW, Esmail R, Bombardier C, Koes BW. Back schools for nonspecific low back pain: a systematic review within the framework of the Cochrane Collaboration Back Review Group. Spine (Phila Pa 1976). 2005;30:2153–63.
79. Furlan AD, Yazdi F, Tsertsvadze A, Gross A, Van Tulder M, Santaguida L, et al. Complementary and alternative therapies for

back pain II. Evid Rep Technol Assess (Full Rep). 2010;194:1–764.
80. Licciardone JC, Aryal S. Clinical response and relapse in patients with chronic low back pain following osteopathic manual treatment: results from the OSTEOPATHIC trial. Man Ther. 2014;19:541–8.
81. Kamper SJ, Apeldoorn AT, Chiarotto A, Smeets RJ, Ostelo RW, Guzman J, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain. Cochrane Database Syst Rev. 2014;9:CD000963.
82. Manchikanti L, Cash KA, McManus CD, Pampati V. Fluoroscopic caudal epidural injections in managing chronic axial low back pain without disc herniation, radiculitis or facet joint pain. J Pain Res. 2012;5:381–90.
83. Manchikanti L, Cash KA, McManus CD, Pampati V, Benyamin RM. A randomized, double-blind, active-controlled trial of fluoroscopic lumbar interlaminar epidural injections in chronic axial or discogenic low back pain: results of 2-year follow-up. Pain Physician. 2013;16:E491–504.
84. Manchikanti L, Singh V, Pampati V, Falco FJE, Hirsch JA. Comparison of the efficacy of caudal, interlaminar, and transforaminal epidural injections in managing lumbar disc herniation: is one method superior to the other? Korean J Pain. 2015;28:11–21.
85. Manchikanti L, Falco FJE, Pampati V, Cash KA, Benyamin RM, Hirsch JA. Cost utility analysis of caudal epidural injections in the treatment of lumbar disc herniation, axial or discogenic low back pain, central spinal stenosis, and post lumbar surgery syndrome. Pain Physician. 2013;16:E129–43.
86. Pauza KJ, Howell S, Dreyfuss P, Peloza JH, Dawson K, Bogduk N. A randomized, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. Spine J. 2004;4:27–35.
87. Freeman BJ, Fraser RD, Cain CM, Hall DJ, Chapple DC. A randomized, double-blind, controlled trial: intradiscal electrothermal therapy versus placebo for the treatment of chronic discogenic low back pain. Spine (Phila Pa 1976). 2005;30:2369–77 discussion 2378.
88. Kapural L, Vrooman B, Sarwar S, Krizanac-Bengez L, Rauck R, Gilmore C, et al. A randomized, placebo-controlled trial of transdiscal radiofrequency, biacuplasty for treatment of discogenic lower back pain. Pain Med. 2013;14:362–73.
89. Lu Y, Guzman JZ, Purmessur D, Iatridis JC, Hecht AC, Qureshi SA, et al. Nonoperative management of discogenic back pain: a systematic review. Spine (Phila Pa 1976). 2014;39:1314–24.
90. Desai MJ, Kapural L, Petersohn JD, Vallejo R, Menzies R, Creamer M, et al. A prospective, randomized, multi-center, open-label clinical trial comparing intradiscal biacuplasty to conventional medical management for discogenic lumbar back pain. Spine (Phila Pa 1976). 2016;41:1065–74.
91. Guo X, Ding WY, Liu L, Yang S. Intradiscal methylene blue injection for discogenic low back pain: a meta-analysis. Pain Pract. 2019;19:118–29.
92. Kallewaard JW, Wintraecken VM, Geurts JW, Willems PC, van Santbrink H, Terwiel CTM, et al. A multicenter randomized controlled trial on the efficacy of intradiscal methylene blue injection for chronic discogenic low back pain: the IMBI study. Pain. 2019;160:945–53.
93. Vallejo R, Zevallos LM, Lowe J, Benyamin R. Is spinal cord stimulation an effective treatment option for discogenic pain? Pain Pract. 2012;12:194–201.
94. Fleege C, Rickert M, Rauschmann M. The PLIF and TLIF techniques. Indication, technique, advantages, and disadvantages. Orthopade. 2015;44:114–23.
95. Ohtori S, Koshi T, Yamashita M, Yamauchi K, Inoue G, Suzuki M, et al. Surgical versus nonsurgical treatment of selected patients with discogenic low back pain. Spine (Phila Pa 1976). 2011;36:347–54.
96. Guo J, Wang Y, Chen ZQ, Liu BW, Yang M, Bai ZL. Effect of radiofrequency versus anterior discectomy and posterior lumbar fixation on discogenic low back pain. J Clin Rehabil Tissue Eng Res. 2007;11:2205–8.
97. Nakashima H, Kawakami N, Tsuji T, Ohara T, Suzuki Y, Saito T, et al. Adjacent segment disease after posterior lumbar interbody fusion: based on cases with a minimum of 10 years of follow-up. Spine (Phila Pa 1976). 2015;40:E831–41.
98. Thavaneswaran P, Vandepeer M. Lumbar artificial intervertebral disc replacement: a systematic review. ANZ J Surg. 2014;84:121–7.
99. Jacobs WC, van der Gaag NA, Kruyt MC, Tuschel A, de Kleuver M, Peul WC, et al. Total disc replacement for chronic discogenic low back pain. Spine (Phila Pa 1976). 2012;38:24–36.
100. Garcia R Jr, Yue JJ, Blumenthal S, Coric D, Patel VV, Leary SP, et al. Lumbar total disc replacement for discogenic low back pain: two-year outcomes of the activL multicenter randomized controlled IDE clinical trial. Spine (Phila Pa 1976). 2015;40:1873–81.
101. Zagra A, Minoia L, Archetti M, Corriero AS, Ricci K, Teli M, et al. Prospective study of a new dynamic stabilisation system in the treatment of degenerative discopathy and instability of the lumbar spine. Eur Spine J. 2012;21:S83–9.