

## General

# Review: Discogenic Back Pain: Update on Treatment

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### Purpose of Review

Lower back pain (LBP) has a lifetime prevalence of 80% in the United States population. Discogenic back pain (DBP), a subcategory of LBP, occurs as a result of the intervertebral disc degeneration without disc herniation. Diagnosis relies on history, physical exam, and imaging such as MRI, provocative discography, or CT discography.

### Recent Findings

Treatment of DBP involves a multifaceted approach with an emphasis on conservative measures including behavioral modification, pharmacologic management, and other non-pharmacologic interventions with invasive therapy reserved for select patients. Due to the paucity of data on the treatment of DBP, treatment also relies on data derived from treatment of chronic LBP (CLBP).

### Summary

Despite the scarcity of data for the treatment of DBP, treatments do exist with varying efficacy for DBP. Novel techniques such as the use of biologics may provide another avenue for treatment though further studies are needed to better evaluate the most efficacious regimen for both novel and existing treatments.

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## INTRODUCTION

Lower back pain (LBP) has a lifetime prevalence of 80% in the United States population, and is the third largest United States healthcare expenditure, behind diabetes and ischemic heart disease.<sup>1,2</sup> Specifically, discogenic back pain (DBP) is a subcategory of back pain defined as pain due to pathology of the disc. Despite the absence of radiographic evidence of disc herniation compressing the spinal column or nerves, the pain in DBP is multifactorial and mainly stems from the degeneration of the intervertebral disc but is also thought to be a result of biomechanical instability, localized inflammation, vertebral endplate pathology, and reinnervation of the area with nociceptive, unmyelinated nerve fibers.<sup>3</sup>

DBP is often referred to as discogenic low back pain (DLBP) due to the frequency of lumbar discs displaying radiographic evidence of degeneration when compared to cervical or thoracic discs. The most commonly affected level of disc degeneration in both men and women is the L4/5 level.<sup>4</sup> Diagnosis of DBP is based on provocative discography or CT discography.<sup>5,6</sup> Treatment options for DBP range from conservative management to more invasive techniques.<sup>5</sup> In this review, we aim to focus on the pathophysiology, presentation, diagnosis of DBP with a special emphasis on treatment.

## PATHOPHYSIOLOGY

DBP primarily results after years of pathologic disc degeneration. Within DBP, there are two types of degeneration, a physiologic degeneration of the disc with absence of back pain, and a pathologic form of disc degeneration known as degenerative disc disease (DDD). It was previously thought that years of repetitive movement and weight bearing were the main cause of DDD; however, a historical cohort study comparing competitive athletes to control subjects demonstrated greater disc degeneration in the lumbar spine of athletes; interestingly, there was less associated back pain in the athlete group than the control group.<sup>7</sup> Twin studies have revealed primary contributing factors to disc degeneration such as genetics and the patient's body mass index.<sup>8</sup> Additionally, environmental factors such as smoking, aging, and injury have been found to contribute and cause disc degeneration.<sup>3</sup> Ultimately, there is a shift towards cell senescence and/or catabolic activity initiating a cascade of events caused by a deficiency of nutrients in the vascularized vertebral endplates leading to a decrease in disc height from loss of hyaluronic acid and water content from the nucleus pulposus and the deposition of collagen fiber.<sup>6,9</sup> These physiologic changes cause cytokine release, inflammation, and microscopic tearing of the annulus fibrosus. The inflammatory cytokine release and tissue damage leads to neovascularization and reinnervation through the annulus fibrosus and into the nucleus pulposus.

The pathophysiology of disc degeneration in DBP can be thought about as occurring in three steps. The first step is the initiation of genomic instability and concomitant ex-

tracellular membrane degradation of the disc.<sup>10</sup> The second step is the body's response to the damage.<sup>10</sup> When the disc has undergone extrinsic or intrinsic damage, there are subsequent changes in cellular homeostasis, including dysregulated pathway signaling (MAPK and NF- $\kappa$ B), which in turn can lead to apoptosis or cell growth arrest.<sup>10</sup>

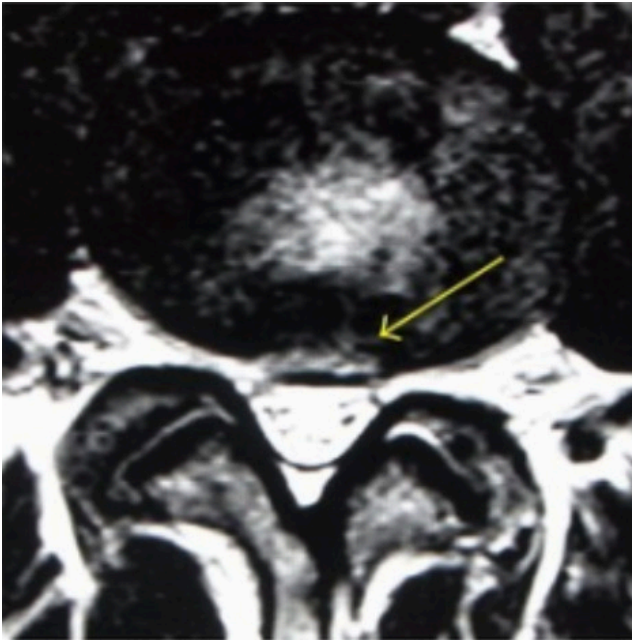
The third and final step can be categorized as loss of disc structure and physiologic function, which can be seen on radiography with loss of disc height and as a hypointensity within the disc on T2 weighted MRI suggesting water and proteoglycan loss within the nucleus pulposus.<sup>10</sup> Though the loss of disc height and hypointensity on T2 weighted MRI can be seen in normal disc aging, it should be considered pathologic disc degeneration when there is neovascularization and reinnervation occurring.<sup>3</sup> Pain will not always be present when there are radiographic signs of disc degeneration; however, when pain is associated with acute and chronic disc degeneration, it is considered DBP. Of note, there is no radiographic herniation of the nucleus pulposus through the annulus fibrosus with DBP.<sup>11</sup>

## EPIDEMIOLOGY AND RISK FACTORS

In the United States alone, it is estimated that more than \$90 billion dollars is spent annually on the diagnosis and treatment of LBP.<sup>12,13</sup> In 2015, the Global Spine Care Initiative reported LBP to be the fourth leading cause of disability-adjusted life years (DALYs) globally.<sup>14</sup> It is estimated that one in three people report having LBP, and the lifetime prevalence ranges from 60-80% of the population.<sup>15</sup> Adding to the existing burden, the prevalence of LBP has been growing exponentially over the past few decades.<sup>14</sup>

LBP is caused by a variety of conditions; however, DBP is the most common cause of chronic LBP (CLBP) in both the young and elderly.<sup>14-17</sup> LBP attributable to DBP has been estimated to be the cause of 26-42% of all LBP cases.<sup>16,18</sup> The variance in this statistic is likely due to the difficulty of diagnosis. Accurate diagnosis is hindered due to the invasiveness of discography, and the concern that it may provoke pain in asymptomatic patients without much benefit. However, the benefit of lumbar discography is that in the case of symptomatic patients, it has a relatively low false positive rate for discogenic pain.<sup>19,20</sup>

DBP is pain secondary to disc degeneration without herniation or disc protrusion.<sup>15,21,22</sup> Therefore, the risk factors for DBP parallels the risk factors of disc degeneration.<sup>18,21,23</sup> The early disc degeneration that is associated with DBP arises from a combination of risk factors from anatomic, genetic, and environmental origins.<sup>23</sup> Specific risk factors for DBP include advanced age, male gender, mechanical loading from trauma, obesity or occupational exposure, smoking, inflammation or infection such as occult discitis or autoimmune discitis, metabolic disorders such as diabetes mellitus, reduced cellularity, and conditions with poor healing.<sup>15,21,23-25</sup> Genetic factors such as the presence of increased levels of cytokine IL1A or MMP13 have also been associated with early disc degeneration and the resultant DBP.<sup>23,25</sup>



**Figure 1. High intensity zone seen in the fifth lumbar vertebra posterior to the posterior longitudinal ligament as a hyperintense zone (yellow arrow) on T2-weighted MRI.**

Image adapted from Sugiura K, et al. Discoscopic findings of high signal intensity zones on magnetic resonance imaging of lumbar intervertebral discs. *Case Rep Orthop*. 2014;2014:245952 using license from <https://creativecommons.org/licenses/by/3.0/>

Since not all disc degeneration leads to DBP, efforts have been made to identify radiographic findings that predict progression to discogenic pain and aid in diagnosis.<sup>19,25-27</sup> One such finding is the presence of Modic changes on MRI, which represent vertebral bone marrow lesions. Modic changes have been demonstrated to have a high specificity for DBP.<sup>25</sup> High-intensity zones (HIZ) on MRI have also been identified as a risk factor for DBP, although with less sensitive and specific (Figure 1).<sup>26</sup> Additionally, CT with provocative contrast discography has demonstrated a relationship between discogenic pain and annular tears.<sup>19</sup>

## PRESENTATION AND DIAGNOSIS

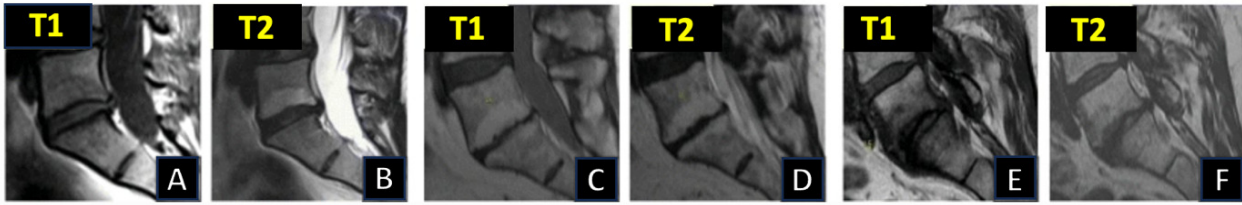
DBP is a specific and localizable form of LBP.<sup>15,24,27</sup> Pain is often provoked with forward flexion of the torso while leaning forward or sitting down, as well as during coughing or sneezing. Flexion is provocative for DBP because it places more compressive stress on the intervertebral disc, and the pain can be worsened with increased axial loading or sitting.<sup>28</sup> Pain may be alleviated by extension while standing up or ambulating.<sup>17,23,24</sup> DBP primarily affects the L5/S1 and L4/L5 discs, respectively.<sup>29</sup> Dermatomal radiation and other neurologic symptoms such as motor weakness, numbness, or incontinence are expected to be absent in DBP as these symptoms are evidence of advanced disc disease involving herniation, nerve compression, or spinal stenosis.<sup>15,17,18,23,30,31</sup> Patients with DBP may report radiation to the buttocks and posterior thighs; however, radiation is not expected to pass below the knees.<sup>23,31</sup>

While the vast majority of DBP affects the lumbar region, it may also affect the thoracic and cervical spine.<sup>14,25,32</sup> In cases of cervical DBP, dizziness has been reported as a presenting symptom. The neural hypersensitization and cytokine release associated with disc degeneration may alter proprioceptive inputs to the vestibular system and cause dizziness.<sup>32</sup>

In DBP, pain is in the mid axis of the spine with lateral movement.<sup>28</sup> This centralization phenomenon can be used to differentiate pain originating in the disc from other cause of low back pain. Sensitivity has been reported to be 46-64% and specificity between 70-100%.<sup>28,33</sup> Its utility as a diagnostic tool for discogenic pain; however, is limited due to lack of standardization and low sensitivity.<sup>28</sup> Bone vibration test is a quick method to screen for DBP by applying vibratory stimuli to spinous process of affected vertebrae triggering a pain response. As a standalone tool, it has moderate sensitivity and specificity but improves when combined with other modalities such as MRI.<sup>28</sup>

MRI is useful for diagnosing DBP with particular attention to HIZ, nuclear signal, disc height, disc contour, and bone marrow intensity change.<sup>33,34</sup> Disc degeneration on T2 weighted MRI appears as hypointense discs due to decreased signal intensity.<sup>28</sup> HIZ on MRI are areas of hypodensity located on posterior annulus fibrosus in lumbar scans. It is theorized that inflammation of the annular fibrous fissure causes the HIZ to appear and is the source of pain in DBP (Figure 1). One study found that TNF-alpha and CD-68 positive cells were higher in number in HIZ than in controls.<sup>35</sup> However, HIZ, has good sensitivity but low specificity for DBP.<sup>36</sup> Modic changes on MRI aid in the diagnosis of DBP as intensity changes on T2 and T1 weighted sequences are used to classify scans of vertebral endplates and subchondral bone into categories describing inflammatory changes, fatty degeneration of bone marrow, and sclerosis of subchondral bone (Figure 2).<sup>36</sup> The combination of different MRI parameters increases its utility as a diagnostic tool.<sup>37</sup>

Provocative discography is an invasive diagnostic procedure in which contrast is injected into nucleus pulposus of a painful disc under pressurized conditions to induce pain. Performing discography at the level of pain may reproduce the patient's pain and serve as a sensitive and specific diagnostic tool. Pain reproduction is attributed to contrast extravasation into annular tears or defects in the endplate associated with disc degeneration and DBP.<sup>18,27</sup> A positive discogram requires reproduction of pain > 6/10 in intensity and at a pressure < 15 pounds per square inch above opening pressure and volume less than 3.0 mL of contrast.<sup>28</sup> This has a high sensitivity and specificity for the diagnosis of DBP. Disadvantages are the invasiveness and a false positive rate of 10%.<sup>38</sup> Of note, patients are at increased risk of accelerated disc degeneration and disc herniation; thus, limiting its use to mainly patients who are planning a surgical procedure to confirm the diagnosis.<sup>39</sup> Discography is safe if specified standards and guidelines are adhered.<sup>40</sup>



**Figure 2. Modic changes seen in T1 and T2 weighted-MRI images. Modic type 1 changes are hypointense on T1 (A) and hyperintense on T2 (B); type 2 are hyperintense on T1 (C) and iso to hyperintense on T2 (D); type 3 are hypointense on T1 (E) and T2 (F).**

Image adapted from Kushchayev SV, et al. ABCs of the degenerative spine. *Insights Imaging*. 2018 Apr;9(2):255-274. using license from <http://creativecommons.org/licenses/by/4.0/>

## DIFFERENTIAL DIAGNOSIS

LBP is common with a reported lifetime prevalence of 80% with a 30% risk of conversion from acute to a chronic back pain.<sup>33</sup> Diagnosing DBP can be challenging as signs and features overlap with other causes of back pain. In the initial evaluation for back pain, systemic causes and red flag symptoms such as malignancy, infection and trauma should be ruled out.<sup>41,42</sup> DBP is marked by axial pain that can in rare occasions radiate to the buttocks, flank and thigh and exacerbated with increased axial load and sitting.<sup>43</sup>

Differentiating DBP from a closely related cause of LBP, vertebrogenic back pain (VBP), can be difficult due to the proximity and overlapping symptoms.<sup>44,45</sup> In VBP, the pain transmission signals are carried via the basivertebral nerve originating from the sinuvertebral nerve, and in DBP, the signals are transmitted via the sinuvertebral nerve.<sup>44,45</sup> VBP ultimately is due to the degeneration of the highly innervated vertebral endplate.<sup>44,45</sup> When the endplates are damaged, proinflammatory mediators and neurogenic growth factors are released promoting proliferation of the basivertebral nerves leading to an increased sensitivity to pain.<sup>44-46</sup> VBP typically presents with axial LBP that can be characterized as deep, burning, and aching in quality; the pain is often worsened with sitting, rising from a seated position, and bending forward at the waist.<sup>44,45</sup> Physical exam focuses on eliciting the pain via flexing movements that place stress on the anterior column with possible tenderness on percussion at the affected vertebral level.<sup>44,45</sup> Diagnosis can be confirmed via MRI which will demonstrate type 1 and 2 Modic changes, with or without endplate damage, and active Schmorl nodes.<sup>44,45</sup>

Other causes of low back pain such as facet arthropathy, paraspinal muscle strain, and spondylolisthesis can present similarly while the presence of radicular symptoms could be mistaken for sacroiliac joint pain and piriformis syndrome. Careful history taking, physical exam, imaging, and laboratory tests can help to make diagnose of DBP. Pain provocation with Valsalva maneuvers, centralization of pain, and pain relief with standing differentiates discogenic pain from other causes of lower back pain.<sup>47</sup> Hallmark of discogenic pain on imaging is intervertebral disc degeneration and the absence of disc herniation. Biomarkers have the potential to act as screening tools to differentiate discogenic

pain from other causes of back pain because inflammatory markers and cytokines are elevated in DBP but not in LBP with sciatica pain.<sup>48</sup>

## TREATMENT

Treatment of DBP involves a multifaceted approach with an emphasis on conservative measures including behavioral modification, pharmacologic management, and other non-pharmacologic interventions with invasive therapy reserved for select patients. Unfortunately, there is a paucity of data concerning the management of DBP; thus, treatment recommendations are often based on data for management of chronic nonspecific back pain.

## PHARMACOLOGIC

Pharmacologic management of discogenic pain relies on the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen with additional agents used as adjuncts. A randomized controlled trial (RCT) that examined 50 patients with CLBP compared 200 mg celecoxib twice daily to 500 mg acetaminophen twice daily and found that celecoxib was significantly more effective for management of symptoms ( $p < 0.05$ ).<sup>49</sup> A multi-center double-blind RCT investigated the role of 60 mg intravenous methylprednisolone, 200 mg intravenous ketoprofen daily, and placebo in addition to a standard oral pain regimen (acetaminophen, nefopam, tramadol, and morphine) in 54 hospitalized patients with acute discogenic sciatica.<sup>50</sup> There was no significant improvement in leg pain across the 3 study arms; however, there was a statistically significant clinical response in leg pain on day 3 of methylprednisolone compared to ketoprofen or placebo.<sup>50</sup>

Gabapentin is a commonly prescribed adjunct for management of DBP. A double-blind RCT compared gabapentin versus placebo in 108 subjects with CLBP over a 12-week period.<sup>51</sup> Participants in the intervention group were titrated to a target dose of 3,600 mg of gabapentin daily or the maximum tolerated dose.<sup>51</sup> Although pain intensity was reduced by approximately 30% from baseline in all participants, there was no significant difference between pain reduction in the intervention and control group; however,

**Table 1. Clinical Efficacy and Safety of Treatments for Discogenic Back Pain**

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions/Limitations
Bedaiwi et al. 2016	Double blind RCT with 50 patients with CLBP, who were given either celecoxib or acetaminophen over 4 weeks.	Celecoxib showed superior efficacy to acetaminophen based on multiple assessment tools (TBP, NBP, ODI, and GRI).	Both groups demonstrated significant improvement; limitations included lack of control group, small sample size, and short follow-up period.
Gastaldi et al. 2019	Double blind RCT comparing daily 60 mg IV methylprednisolone, 200 mg IV ketoprofen, vs placebo in 54 hospitalized patients with acute discogenic sciatica.	No significant improvement in leg pain across the 3 study arms. Statistically significant clinical response in leg pain on day 3 of methylprednisolone compared to ketoprofen or placebo.	No significant analgesic effect in leg pain across 3 groups. There may be benefit to IV methylprednisolone early in course of admission. Further data is needed to better understand the effect of oral glucocorticoids or role later in disease course.
Atkinson et al. 2016	12 weeks, 2 arm double blind RCT comparing 108 patients receiving gabapentin or placebo.	No significant improvement between groups regarding analgesia or disability.	Treatments were not effective; however, the study was limited by a small sample size, high participant attrition rate, and additional comorbid disease processes.
Cashin et al. 2021	Meta-analysis of 31 trials (6,506 participants) examining non-benzodiazepine antispasmodics and placebo in pain intensity and disability.	Short course ( $\leq 2$ week) of non-benzodiazepine antispasmodics decreased pain intensity but not disability compared to placebo.	Minimal efficacy; limitations included lack of standardization, long-term efficacy, and safety.
Hirase et al. 2021	Systematic review of 5 studies comparing duloxetine to placebo.	Effective reduction in pain and improved functional status with minimal adverse events.	Duloxetine is an effective medication for reducing pain and disability; limitations of the review included heterogenous outcome measures and study criteria, as well as potential confounding comorbid pain conditions.
Urquhart et al. 2018	RCT of 146 participants evaluating efficacy of low dose amitriptyline and. benzotropine.	No significant reduction in pain intensity at 3 or 6 months. Statistically significant reduction of disability at 3 months and reduction in pain that was not significant at 6 months.	No significant primary outcome but possible minimal to moderate benefit; limitations included heterogenous sample group, small sample size, lack of long-term efficacy, and safety analysis.
Boya et al 2021	Meta-analysis of 23 RCTs including 8,420 participants with CLBP.	Oxymorphone, tramadol with acetaminophen, and buprenorphine were all more effective than placebo in achieving both a 30% or 50% decrease in baseline pain with oxymorphone as the overall most effective agent.	Short-term trial of opioid analgesics may be reasonable but limited by the side effect profile of opioids.
Hayden et al. 2021	Meta-analysis of 249 RCTs assessing role of exercise in improvement of pain and functional status in adults with CLBP.	Exercise is more effective than the control group (no treatment, usual care, or placebo) for CLBP.	Moderate-level evidence; limitations include risk of bias, difficulty blinding intervention versus control group and heterogeneity.
Yang et al. 2022	Systematic review of 22 RCTs assessing efficacy of CBT.	CBT was effective at improving disability, pain, and fear avoidance immediately after intervention, particularly in conjunction with other treatment modalities.	Treatment is moderately beneficial; limitations include lack of standardization, lack of blinding, and data restricted to English only studies.
Huang et al. 2019	RCT of 46 participants with discogenic sciatica comparing acupuncture versus sham acupuncture across 12 sessions over 4 weeks.	Significant improvement in primary outcome (change from baseline in mean VAS scores for leg pain). Secondary outcomes included change from baseline mean VAS for leg pain or lower	Evidence to support improvement of leg pain in individuals with discogenic sciatica. Further studies needed with larger sample size, treatment period, and follow-up

Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions/Limitations
		back pain, ODI, and SF-36 scores.	needed to fully assess impact of acupuncture.
Resende et al. 2018	Meta-analysis of 4 RCTs including 585 patients assessing role of TENS or IFC versus placebo or control for pain intensity and disability in CLBP and/or CNP.	TENS/IFC reduced pain intensity and disability in CLBP and/or CNP compared to placebo or control group during therapy but not after therapy or at 1- or 3-month follow-up.	Overall results inconclusive about effect. Limited by study heterogeneity, low quality studies, and insufficient sample size.
Kallewaard et al. 2020	Prospective study of 20 patients who underwent DRG stimulation for DBP.	Improvement in DBP at 12-month follow-up, reduction in disability at 6- and 12-month follow-up and improvement in quality of life at 12-month follow-up.	DRG stimulation may be effective at improving pain scores and quality of life and reducing disability in patients with DBP. Large-scale RCTs should be performed to better understand true effect.
Manchikanti et al. 2020	Meta-analysis of 15 RCTs on efficacy of lidocaine epidural injections with or without steroids for spinal pain.	Significant improvement of pain and functionality short- and long-term with epidural injections containing lidocaine; no significant difference with or without steroids.	Moderate quality evidence to support use of lidocaine epidural injections for management of spinal pain; further studies are needed to further elucidate role of steroids.
Deng et al. 2021	Meta-analysis of three RCTs evaluating methylene blue disc injection vs control for pain and disability in discogenic back pain.	Significant improvement in pain at 3- and 6-month follow-up in intervention group compared to control. Significant improvement in ODI at 4-6 week and 3-month follow-up but not 6-month follow-up in intervention group compared to control.	Methylene blue disc injection is an effective treatment for improving pain and reducing disability short-term for discogenic back pain.
Xu et al. 2021	Meta-analysis of 6 prospective studies comparing short-term (159 participants) and long-term (675 patients) outcomes in participants with CLBP secondary to DJD who underwent lumbar spinal fusion versus nonoperative management	Spinal fusion surgery did not improve pain or disability outcomes compared to nonoperative management short- or long term.	Further large scale, high-quality RCTs needed to further assess efficacy of spinal fusion surgery. Careful consideration should be used when considering spinal fusion surgery versus nonoperative management.
Koenders et al. 2019	Meta-analysis of 25 prospective cohort studies including 1,777 participants with lumbar degenerative disorders who underwent lumbar spinal fusion.	Lumbar spinal fusion significantly improved back pain, leg pain, and disability at 24-month follow-up compared to pre-surgical assessment.	Significant improvement in pain and disability after first-time lumbar spinal fusion; Further studies needed to assess long-term outcomes.
Siepe et al. 2014	Prospective single-center study with 201 patients who underwent total lumbar disc replacement for refractory lumbar DJD.	Significant improvement in pain and disability at 3-, 6- and 12-month follow-up compared to baseline. Marginal but statistically significant worsening of pain score at 48-month follow-up and beyond. Stable patient satisfaction post-operatively.	Total lumbar disc replacement is reasonable to consider for refractory lumbar degenerative joint disease.
Patil et al. 2018	Prospective study of 300 patients with single-level herniated disc who underwent microendoscopic discectomy.	Significant improvement in VAS and MSS scores at 7-day and 6-month follow-up compared to baseline. Post-operative complications in 6% of patients.	Microendoscopic discectomy is an effective treatment for discogenic pain. Limitations include risk of post-operative complication.
Lee et al. 2017	Retrospective study of 81 patients who underwent PELAN for DBP.	Significant reduction in NRS and ODI% in short-term (3-4 week) and long-term ( $\geq 12$ month) follow-up. Good or excellent Mcnab response in 61% and 65.2% of patients at short- and long-term follow-up, respectively.	PELAN has good short- and long-term outcomes for DBP and could be considered in patients with refractory symptoms.



Author (Year)	Groups Studied and Intervention	Results and Findings	Conclusions/Limitations
Sanapati et al. 2018	Meta-analysis of 21 studies on injection of biologics (MSCs and PRP) for lower back pain.	Level 3 evidence to support use of disc injections of MSCs and PRP for lower back pain. Level 4 evidence (limited) in favor of epidural and lumbar facet joint biologic injections.	Low level data that biologic injections may be effective for management of lower back pain. Further large-scale high-quality RCTs needed to further assess.
Hunter et al. 2021	RCT consisting of 218 patients treated with viable allogeneic disc tissue supplementation.	Younger patients (< 42 years of age) experienced more functional benefits in the treatment group with no difference between the treatment and control in older patients (> 42 years of age).	Viable allogeneic disc tissue supplementation is a promising treatment in younger patients. Limitations include the use of saline as a control as it can elicit a clinical response.

## Abbreviation Key:

CLBP: chronic lower back pain, DBP: discogenic back pain, DJD: degenerative joint disease, DRG: dorsal root ganglion, GRI: Guyatt's responsiveness index, MSCs: mesenchymal stem cells, MSS: modified Suezawa and Schreiber, NBP: nocturnal back pain, NRS: numeric rating scale, ODI%: Oswestry disability index %, PELAN: percutaneous endoscopic lumbar annuloplasty and nucleoplasty, PRP: platelet-rich plasma, RCT: randomized control trial, SF-36: 36-items short form survey, TBP: total back pain, VAS: visual analog scale.

this data is limited by a small sample size and high attrition rate.<sup>51</sup>

Muscle relaxants are another commonly used adjunct for DBP. A meta-analysis of 31 RCTs found that short courses of non-benzodiazepine antispasmodics for acute LBP yielded a significant reduction in pain compared to the placebo; however, it did not find improvement in disability and may be associated with an increase in adverse events.<sup>52</sup> Moreover, antidepressants may be another effective adjunct for the management of DBP. A systematic review that examined data from 5 RCTs on the effectiveness of duloxetine demonstrated that duloxetine was an effective treatment for management of CLBP with 60 mg daily as the recommended dose based on efficacy and adverse event profile.<sup>53</sup> A double-blind RCT studied the effectiveness of tricyclic antidepressants on management of CLBP compared low-dose amitriptyline (25 mg daily) to benztropine (1 mg daily) in 146 participants with CLBP.<sup>54</sup> There was not a statistically significant reduction in pain at 3 or 6 months.<sup>54</sup> However, there was a statistically significant improvement in disability in the amitriptyline group at 3 months and a reduction in pain intensity at 6 months that was not significant, suggesting that amitriptyline may be a reasonable treatment option in select patients.<sup>54</sup>

## NON-PHARMACOLOGIC

While medical therapy with anti-inflammatory medications remain the mainstay of symptom alleviation, physical therapy should be incorporated into DBP treatment regimens, with emphasis placed on strengthening and stabilization of pelvic and core muscle groups.<sup>15-18,21,23,30,55</sup> A meta-analysis of 249 RCTs found that exercise therapy is significantly more effective for management of CLBP compared to no treatment, usual care, or placebo.<sup>56</sup> Furthermore, cognitive behavioral therapy (CBT) may be beneficial in the treatment of DBP. A meta-analysis of 22 RCTs evaluated the efficacy of CBT for treatment of CLBP comparing CBT versus control (*i.e.*, usual care, physical therapy, and drug therapy) and found that patients treated with CBT had a statistically significant improvement in regard to disability,

fear avoidance, and self-efficacy after intervention; however, there was no significant improvement at 3-, 6-, or 12-month follow-up. Subgroup analysis suggested that CBT was most effective when used in combination with other interventions.<sup>57</sup>

Moreover, acupuncture can be used as an adjunct for DBP. One RCT that evaluated acupuncture versus sham acupuncture across 12 sessions over 4 weeks in 46 participants with discogenic sciatica found improvement in weekly mean visual analog scale (VAS) scores from baseline for leg pain in the intervention group.<sup>58</sup> Secondary outcomes including change from baseline mean VAS for leg pain or lower back pain, Oswestry Disability Index (ODI) scores, and 36-Item Short Form Health Survey (SF-36) scores were not statistically significant.<sup>58</sup>

## MINIMALLY INVASIVE

A recent meta-analysis of 7 RCTs including 655 participants found that transcutaneous electrical nerve stimulation (TENS) or interferential current (IFC) significantly improved pain intensity and reduced disability compared to placebo or control in individuals with CLBP and/or neck pain (CNP) during treatment but not immediately after or at 1- or 3- month follow-up.<sup>59</sup> Another study of 20 patients found that dorsal root ganglion stimulation improved pain and quality of life at 12-month follow-up and disability at 6- and 12-month follow-up in patients with DBP.<sup>60</sup>

Spinal injections are often used for DBP that do not respond to conservative measures. A meta-analysis of 15 RCTs demonstrated moderate level evidence that epidural injections with lidocaine was effective for short- and long-term pain relief and improvement of functionality in patients with spinal pain; however, there was not a significant difference between injections with or without steroids.<sup>61</sup> A meta-analysis of 3 RCTs found that methylene blue disc injections do significantly improve pain at 3- and 6-month follow-up and disability at 4-6 week and 3-month follow-up compared to control.<sup>62</sup>

An alternative option for the management of DBP is regenerative medicine. While regenerative therapies such as

biologics and stem cell therapies hold much promise, outcomes in clinical trials have yet to demonstrate meaningful results.<sup>15,17,21-23,63</sup> Interestingly, there does seem to be an age-dependent response to allogeneic stem-cell therapy for the treatment of DBP.<sup>63</sup> A meta-analysis of 21 studies found evidence that injection of medicinal signaling cells or mesenchymal stem cells and platelet-rich plasma may have a beneficial role in management of LBP; however, further RCTs are needed to fully evaluate their efficacy.<sup>64</sup> The use of viable allogeneic disc tissue derived from cadavers has demonstrated promising results in young patients (< 42 years of age) who are afflicted with DBP.<sup>65,66</sup> Unfortunately, in older patients (> 42 years of age) there was no difference between the control and allogeneic supplementation group plus.<sup>65</sup> The study was limited by the use of saline injection as the control as it can elicit a clinical response.<sup>65,66</sup> Fortunately, saline does not retain water due to the absence of proteoglycans; thus, patients were crossed over to the treatment group and had positive results not requiring retreatment at 36-month follow-up.<sup>65,66</sup>

#### INVASIVE

Data regarding efficacy of lumbar spinal fusion for CLBP is mixed. A meta-analysis of 6 studies comparing lumbar fusion versus nonoperative management for CLBP secondary to degenerative joint disease did not find a significant improvement in 24-month follow-up or disability both short- or long-term.<sup>67</sup> Conversely, a meta-analysis of 25 prospective cohort studies including 1,777 participants with lumbar degenerative disorders who underwent first-time lumbar spinal fusion found significant improvement in back pain, leg pain, and disability at 24-month follow-up compared to pre-surgery.<sup>68</sup>

Both standard open discectomy and minimally invasive discectomy are options for treatment of DBP. A prospective study that evaluated the efficacy of total lumbar disc replacement in 201 patients found significant improvement in pain and disability at 3-, 6-, and 12-month follow-up compared to baseline; however, there was a significant worsening in pain scores after 48-month follow-up.<sup>69</sup> The role of minimally invasive discectomy was investigated in

a study with 300 patients with DBP secondary to single-level herniated disc which revealed a significant improvement of symptoms based on VAS and modified Suezawa and Schreiber clinical scoring system (MSS) scores.<sup>70</sup> Finally, a retrospective study which evaluated 89 patients who underwent percutaneous endoscopic lumbar annuloplasty and nucleoplasty (PELAN) for DBP demonstrated improved outcomes based on the numeric rating scale, Oswestry disability index percent, and modified Macnab criteria at both short-term and long-term follow-up.<sup>71</sup>

Despite treatment, DBP is a chronic condition which can be resistant to long-term amelioration.<sup>22,30,72</sup> Over 68% of patients with DBP reported ongoing pain despite non-surgical treatment; nevertheless, the progression to more serious conditions such as disc herniation, nerve root compression, or spinal stenosis in DBP was low at the 4-year follow-up period.<sup>72</sup>

#### CONCLUSION

Healthcare spending in the United States on LBP is upwards of \$87.6 billion per year, making it the third most expensive disease, behind diabetes and ischemic heart disease.<sup>2</sup> DBP, a subcategory of LBP, is an often difficult to diagnosis with treatments having limited efficacy. Further research studies are needed to better define which patient population would benefit from the different types of treatment. Furthermore, additional studies are needed to fully appreciate novel options such as regenerative medicine and viable allogeneic disc tissue which may be an alternative treatment avenue for select groups of patients.

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#### AUTHOR CONTRIBUTIONS

All authors were involved in the writing and editing of the manuscript.

#### DISCLOSURES

There are no conflict of interests with the authors.



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