Pain Physician 2024; 27:401-413 • ISSN 1533-3159

Narrative Review

Treatment Gaps and Emerging Therapies in Lumbar Disc Herniation

Douglas P. Beall, MD[1], Kee D. Kim, MD[2], Kevin Macadaeg, MD[3], Kianoush Donboli, MD[4], Kinsuk Chauhan, MD[4], Mohan Sowlay[4], Amy Guo, PhD[4], and Alexander Vaccaro, MD, PhD[5]

From: [1]Comprehensive Specialty Care, Edmond, OK; [2]Department of Neurological Surgery, UC Davis, Cannery Building, Spine Center, Sacramento, CA; [3]Indiana Spine Group, Carmel, IN; [4]Ferring Pharmaceuticals, Inc., Parsippany-Troy Hills, NJ; [5]Rothman Orthopaedic Institute, Philadelphia, PA

Address Correspondence:
Douglas P. Beall, MD
Comprehensive Specialty Care
1023 Waterwood Parkway
Edmond, OK 73034
E-mail: db@clinrad.org

Disclaimer: There was no external funding in the preparation of this article.

Conflict of interest: See page ### for all conflicts.

Article received: 03-25-2024
Revised article received: 04-09-2024
Accepted for publication: 05-23-2024

Free full article: www.painphysicianjournal.com

Background: Lumbar disc herniation (LDH) occurs when the central disc material, primarily the nucleus pulposus, is displaced beyond the outer annulus, compressing the spinal nerve roots. LDH symptoms, including radicular leg pain, radiculopathy, and low back pain, are associated with considerable disease burden and the significant utilization of health care resources.

Objectives: Provide overview of the current treatment landscape for LDH, identify unmet needs, and describe emerging treatments.

Study Design: Narrative literature review.

Methods: A review of literature concerning available LDH treatments and associated outcomes was conducted in PubMed to identify areas of unmet need. Some key words included "lumbar disc herniation," "radicular leg pain," "sciatica," "treatment," "therapy," and "burden."

Results: For patients who do not respond to conservative therapy, epidural steroid injections (ESIs) are widely used for persistent LDH symptoms. While ESIs provide short-term improvements in radicular pain, evidence that ESIs bestow sustained benefits is limited. ESIs are not approved by the US Food and Drug Administration (FDA) and, in rare cases, carry risks of infection and neurological injury, as well as the potential for long-term systemic effects of glucocorticoids. In cases when nonsurgical treatment fails to relieve symptoms, lumbar discectomy can provide rapid pain relief; however, in addition to the risk of intraoperative complications, the long-term consequences of lumbar discectomy may include recurrent pain or herniation, revision discectomy, loss of disc height, and Modic changes. Treatments for LDH in late-stage clinical development include sustained-release ESI formulations and a novel agent for chemonucleolysis, a nonsurgical method of minimizing the volume of the displaced nucleus pulposus. Emerging minimally invasive therapies that address the underlying pathophysiology of the disease have the potential to bridge the gap between symptomatic treatments and surgery.

Limitations: Because this paper was a narrative review, literature search and selection processes were not systematic in nature. The evidence regarding the long-term efficacy of some treatments, such as discectomy, was limited by the high rates of crossover between the treatment groups.

Conclusions: The lack of sustained benefits associated with ESIs and the risks associated with surgery underscore the unmet need for novel, minimally invasive interventional therapies able to address the underlying nerve root compression in LDH.

Key words: Lumbar disc herniation, radicular leg pain, lumbar radiculopathy, epidural steroid injection, surgery, microdiscectomy, chemonucleolysis, condoliase, intradiscal therapy, minimally invasive treatment

Pain Physician 2024: 27:401-413

Lumbar disc herniation (LDH) is considered the most common cause of lumbar radiculopathy (e.g., sciatica), accounting for an estimated 90% of cases (1,2). LDH is defined as displacement of central disc material (nucleus pulposus and/or annulus fibrosis) beyond the normal margins of the intervertebral disc. LDH presents clinically as radiculopathy when the herniated material compresses or irritates the spinal nerve roots, producing pain that radiates to the leg and foot and can be associated with neurological signs and symptoms (3,4). Patients with lumbar radiculopathy experience more pain, greater disability, more use of health care, and poorer quality of life than those with nonspecific low back pain (5,6). Disc herniations are considered contained when the outer annulus/posterior longitudinal ligament is intact (e.g., protrusion, subligamentous extrusion) or uncontained when such covering is absent (e.g., transligamentous extrusion, sequestration). Herniations are further classified based on the shape of the displaced material (protrusion vs extrusion; Fig. 1), discontinuity with the parent disc (sequestration), and the location of the herniation (7). The estimated prevalence of LDH is 1% to 3%, occurring most commonly in people aged 30 to 50 years (8,9). Approximately 95% of all disc herniations occur at L4/L5 or L5/S1, with herniations above this level more common in people over 55 years of age (10).

While many people with LDH will recover independently of treatment (3), a subset of patients experience persistent radiculopathy that can be difficult to manage (11). Symptomatic treatments, including epidural steroid injections (ESIs), can provide short-term pain relief but do not address the underlying cause of radicular leg pain by decompressing the nerve root. Surgery may resolve the underlying causes of LDH, but such procedures come with risks of complication. Ultimately, the optimal LDH treatment will be determined on an individual basis through collaborative decision-making between the patient and physician, since evidence remains unclear as to which treatment course is superior. There remains a significant unmet need for nonsurgical, minimally invasive, safe interventions for LDH that address the underlying nerve compression and thus provide lasting relief from associated symptoms. In this narrative review, we will summarize the current treatments for LDH, identify unmet needs in LDH treatment, and discuss the evolving landscape, including emerging LDH treatments that have the potential to bridge gaps and expand the armamentarium of LDH treatments.

Conservative Therapy

First-line treatment for radicular leg pain caused by LDH is conservative care for a minimum of 4 to 6 weeks (12,13). Approximately 90% of patients with LDH will have their symptoms resolve spontaneously or with conservative care (13,14). Most patients begin with a combination of nonpharmacological and pharmacological treatment approaches (15). Nonpharmacological management strategies include rest, physical therapy, massage, acupuncture, chiropractic spinal manipulation therapy, and transcutaneous electrical nerve stimulation (TENS) (13). These commonly used interventions have limited high-quality evidence to support their effectiveness for lumbar radiculopathy (14,16).

Pharmacologic treatments for LDH symptoms include nonsteroidal anti-inflammatory drugs (NSAIDs), anticonvulsants (e.g., gabapentin), antidepressants, opioids, and benzodiazepines. While most pain medications have been evaluated in clinical trials, evidence of their efficacy remains limited due in part to variability in the quality of trials and study parameters (17). A Cochrane review based on predominantly low-quality randomized controlled trials (RCTs) found that NSAIDs were no more effective than placebos in reducing radicular leg pain or disability. Several small trials of low methodological quality suggested NSAIDs were more effective than placebos on patient-reported global improvement (18). Adverse effects of NSAIDs are typically mild but include gastrointestinal problems (18). While some guidelines recommend anticonvulsants for the treatment of chronic neuropathic pain (19), more recent guidelines specific to sciatica and LDH do not recommend gabapentinoids (3,20). Several clinical trials, including a recent RCT (21), found no benefit associated with the use of anticonvulsants for lumbar radiculopathy (17). Concerns have been raised over the growing abuse and misuse of gabapentinoids, which are frequently prescribed off-label (22). While opioids provide short-term pain relief, evidence on the benefits of long-term opioid administration is lacking. Opioids should be used cautiously given their high risk of abuse and dependence and the high rate of opioid-related deaths in the US (10,23,24). Side effects of opioids include nausea, vomiting, constipation, drowsiness, memory loss, and dizziness (17,19,25). Recently, the UK National Institute for Health and Care Excellence (NICE) recommended against the use of gabapentinoids, benzodiazepines, or opioids for sciatica, given the insufficient evidence of effectiveness and the potential lon-

ger-term harms associated with those medications (20). Although conservative management is recommended as the initial treatment for lumbar radiculopathy, the available evidence from systematic reviews and RCTs has not revealed a consistently efficacious conservative treatment (17,26).

Epidural Steroid Injections

When conservative therapy is ineffective, multiple clinical practice guidelines and pain societies recommend ESIs as a potential treatment for persistent lumbar radiculopathy (10,19,27). The total number of ESIs performed annually in the US is estimated to exceed 9 million (28,29). Corticosteroids exert anti-inflammatory effects through a variety of mechanisms, including the inhibition of pro-inflammatory cytokine activity (9). ESIs are performed using a variety of methods, and the risks of ESIs vary depending on the steroid preparation and approach to the epidural space (9,30).

Despite the wide use of corticosteroids, the US Food and Drug Administration (FDA) has not approved them for epidural administration. Risks of ESIs include the potential for infection from contaminated sources as well as serious neurological injury due to needle placement. In 2002 and 2012, multistate outbreaks of fungal meningitis and other infections were caused by the contamination of methylprednisolone acetate preparations produced in compounding pharmacies (29,31). In 2014, the FDA warned that injection of corticosteroids into the epidural space may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death (32). The FDA requires a class label warning on injectable corticosteroid products stating that "serious neurological events, some resulting in death, have been reported with epidural injection of corticosteroids" and that the "safety and effectiveness of epidural administration of corticosteroids have not been established and corticosteroids are not approved for this use" (33).

While there is consensus that ESIs provide rapid short-term pain relief, the long-term efficacy of ESIs for lumbar radicular pain is still a subject of debate and may depend on evidence synthesis methodology (34,35). Recently, a Cochrane systematic review and meta-analysis of placebo-controlled RCTs in patients with radicular leg pain concluded that there was moderate quality evidence that ESIs were more effective than placebos in reducing leg pain and disability over the short term

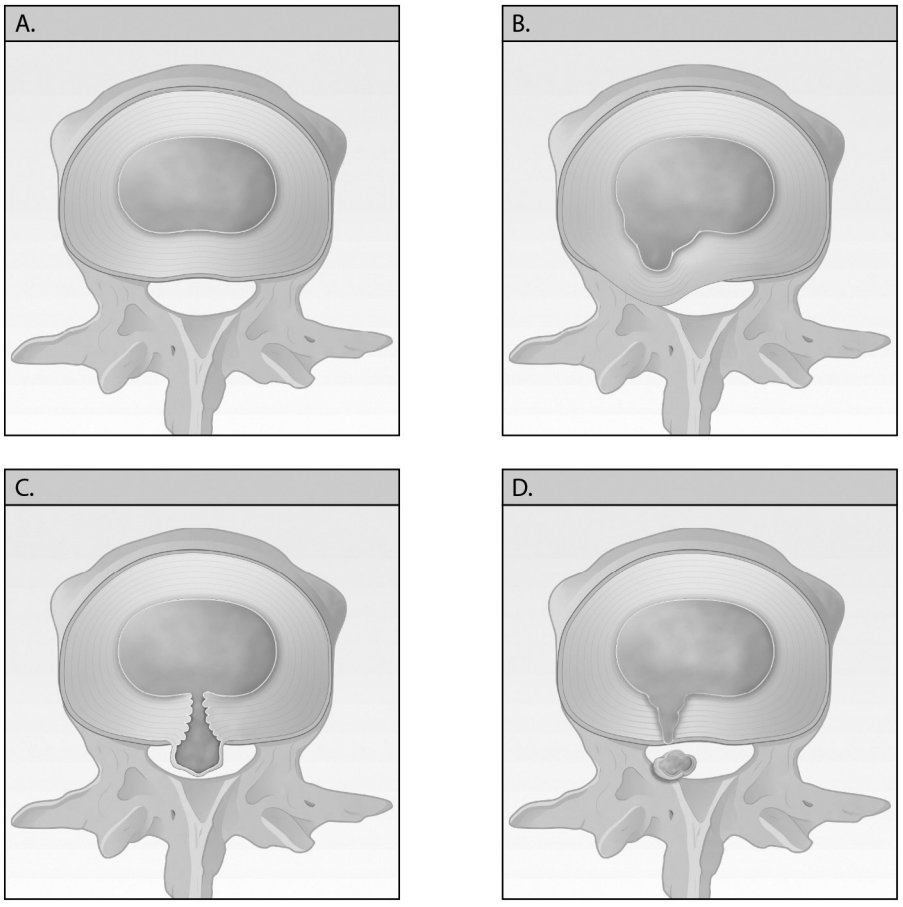

Fig. 1. *Schematic representation of a normal disc and types of disc herniation. A) Normal disc. B) Protrusion. C) Extrusion. D) Sequestration.*

of 3 months (35). The short-term effects were modest (< 10 points on a 0-100 scale), and ESIs were not more effective than placebos at reducing leg pain in the intermediate (> 3 to ≤ 12 months) or long term (> 12 to 30 months). Other systematic reviews of RCTs assessing the efficacy of ESIs as treatments for LDH or sciatica generally reported similar findings of greater small, short-term improvements in leg pain and/or disability than were seen with placebos (36-38). In a re-evaluation of the same trials reviewed by the Oliviera et al Cochrane study, Manchikanti et al used a different methodology and defined local anesthetics as "active controls" rather than "true placebos" (34). Based on a single-arm meta-analysis of 4 active-controlled trials, Manchikanti et al concluded that there was moderate evidence of improvement in pain and disability at the 6- and 12-month follow-ups with both ESIs and local anesthetics and with local anesthetics alone (34). Another systematic review of RCTs found that ESIs (as opposed to control injections) provided a weak surgery-sparing effect in the short term but not the long term (39), a finding consistent with the perception of ESIs' benefits as transient.

Few studies have examined longer-term outcomes (> one year) of ESIs in patients with LDH who have no other concomitant spinal pathologies. In a small RCT follow-up study of patients with LDH-caused radicular pain who received transforaminal ESIs after not responding to conservative care, the majority of patients (77%) experienced a recurrence of pain at the 5-to-9-year follow-up (40). Almost a quarter of patients (23%) reported receiving additional transforaminal ESIs, and almost half (49%) underwent spine surgery (40). As was consistent with these findings, in a large claims database study of LDH patients who received lumbar ESIs, 34% received a second ESI within 6 months, and 44% received a second ESI by 5 years (41). Additionally, 13.5% of patients with LDH progressed to surgery within 6 months of the index ESI (41). An analysis of patients with radicular pain who received repeat transforaminal ESIs (2-3 injections within 12 months) found a decrease in effectiveness with subsequent injections relative to the index injection (42). While limited, the available evidence on long-term outcomes of ESIs for LDH patients does not suggest that the procedures offer sustained benefits.

The overall complication rate of fluoroscopically directed lumbar ESIs is low (< 1%) (43,44). Most complications are considered minor, including vasovagal reactions, exacerbation of pain, headache, and dural puncture (43,45). Serious complications of permanent neurological injuries following ESIs are rare and limited to case reports. Among lumbar ESIs, paraplegia was reported most extensively in association with the transforaminal approach, and all cases involved particulate steroids (45). In collaboration with an FDA Safe Use Initiative, a multidisciplinary group of experts introduced safeguards in 2015 to reduce the risk of severe neurological complications. As a result, recommended practices include radiographic guidance with appropriate lateral or oblique views to mitigate the risk of intravascular injections. For lumbar transforaminal injections, a nonparticulate steroid (dexamethasone) was recommended as a first-line agent, although particulate steroids were acceptable in certain situations, such as when a patient failed to improve after the introduction of nonparticulate formulations (45).

Systemic absorption of glucocorticoids after an ESI poses additional risks, including hypothalamic-pituitary-adrenal (HPA) axis suppression, immunosuppression, elevated blood glucose levels, and deleterious effects on bone health (46,47). ESI injections have been shown to reduce serum cortisol for several weeks after injection (48,49). The extent of HPA axis suppression differs by corticosteroid type, with some less water-soluble formulations (e.g., methylprednisolone) causing a 41% reduction 3 weeks after a single ESI (49). Evidence from large national database studies of Medicare patients (≥ 65 years) who underwent lumbar decompression surgery suggests that preoperative lumbar ESIs increase the risk of postoperative infections (50,51). Patients who received ESI within one month of lumbar decompression surgery had a threefold higher risk of postoperative infection, while those receiving lumbar ESI one to 3 months before surgery had an almost doubled risk of infection compared with matched controls who did not receive lumbar ESIs (51).

ESIs have been shown to affect glucose homeostasis in individuals with and without diabetes (47). In a small prospective study of patients with type 1 or type 2 diabetes, ESI administration resulted in a significant but transient increase (79%) in blood glucose levels (52). In addition, it is well established that oral and intravenous (IV) glucocorticoids suppress bone formation, accelerate bone loss, and increase the risks of fractures and osteoporosis (46,53). While ESIs involve systemic exposure to a far lesser extent than do oral and IV glucocorticoids (46), several studies suggest that ESIs may have detrimental effects on bone health. Patients who received lumbar ESIs had a greater risk of vertebral fracture than did propensity score-matched controls

who did not receive lumbar ESIs (54). Additionally, a small prospective, controlled study recently found that postmenopausal women who received ESIs showed significant and sustained reductions in bone formation markers than did controls for up to 12 weeks (48).

Patients who receive repeat ESIs may face additional risks of prolonged or cumulative exposure. A large retrospective study showed that each successive lumbar ESI significantly increased the patient's risk of vertebral fracture (relative risk of 1.21 vs. matched controls) (54). Complementing these findings, postmenopausal women who received repeat ESIs within one year showed greater suppression of the bone formation marker procollagen type I N-terminal propeptide (P1NP) than did those who received a single injection (48). In addition, repeat fluoroscopic procedures could increase cumulative radiation exposure, which could in turn potentially increase the risk of cancer (55,56). While the available data are limited, these findings support a cautious approach to ESIs, particularly in patient populations at greater risk for systemic effects, such as people with diabetes and postmenopausal women. Additional well-controlled studies are needed to better understand the systemic effects and potential long-term sequelae of ESIs, especially considering their relatively short-term benefits.

Surgery

When nonsurgical treatment fails to relieve LDH symptoms (as happens in ~10% of cases), lumbar discectomy is an effective procedure in which removal of the herniated disc and/or disc fragments decompresses the neural structures and thus relieves radicular leg pain (57,58). While at least 6 weeks of conservative care are recommended before considering surgery (13), there is no consensus for the optimal timing of the discectomy (1,59). One exception is cauda equina syndrome, a rare complication of LDH that is an absolute indication for immediate surgical intervention (60). Another exception is patients with drop foot, since they have been noted to experience better outcomes when surgical intervention occurs earlier (61).

Evidence from RCTs indicates that discectomy provides a greater reduction in leg pain than does nonsurgical treatment, but these benefits diminish over time (58). Several randomized trials comparing surgery with conservative care found that surgery improved leg pain in the short term (62,63). Early surgery (i.e., 6-12 weeks after symptom onset) is associated with faster short-term pain relief compared to conservative treatment, but the outcomes are similar by the one-year follow-up (59,64). In patients with a longer duration of LDH symptoms (4-12 months), conventional microdiscectomy was superior to nonsurgical care at improving leg pain at the 6-month follow-up (65). Long-term outcomes of discectomy are less clear, since high rates of crossover between discectomy and nonoperative groups (40%-50% at 8 years) have complicated the interpretation of results (66). In the 8-year follow-up of the SPORT trial, Lurie et al did not observe significant differences between discectomy and nonoperative care in the intent-to-treat analysis for primary outcome measures of pain, physical function, or disability. The surgery group did report more favorable outcomes in the discomfort caused by the sciatica, satisfaction with symptoms, and self-rated improvement (66).

Open microdiscectomy is considered the gold standard for removing disc herniations and is the most commonly performed surgical procedure for LDH (67). During a conventional open microdiscectomy procedure, the patient is under general anesthesia, and a small vertical incision is made in the lower back. Under microscopic magnification, surrounding muscles, ligaments, and/or bone (laminotomy) are spread or removed to facilitate the removal of the herniated fragment. Less invasive surgical approaches have been developed to reduce iatrogenic damage to muscles, ligaments, and other structures. Tubular discectomy uses a muscle-splitting tubular retractor system through a small incision, while endoscopic disc surgery requires the percutaneous introduction of a thin tubular device containing the optical system and a working channel (68,69). Both tubular and endoscopic lumbar discectomy have been found to produce clinical results comparable to conventional open microdiscectomy, since approximately 77% to 85% of patients treated with any of these techniques were considered to have recovered from leg pain (69,70). Some studies have found endoscopic discectomy to be associated with shorter hospital stay and shorter operating times, but high-quality studies are lacking (70,71).

The benefits of discectomy must be weighed against the risks of long-term consequences, such as recurrence of pain, and surgical complications. Meta-analyses have shown that overall complication rates are approximately 13% to 17% for open microdiscectomy, 13% to 21% for microendoscopic discectomy, and 6% to 11% for percutaneous microdiscectomy (72,73). The most common intraoperative complication of discectomy is durotomy (dural tearing), which occurs at report-

ed rates of 1.3% to 3.5% when primary discectomies are performed (74). Additional complications include wound complications (e.g., infection), hematoma, new or worsening neurological deficit, and nerve injury (72).

Long-term consequences of discectomy include the recurrence of pain, reherniation, and reoperation, as well as related structural changes such as loss of disc height and Modic changes. Approximately a quarter (23%-28%) of patients will experience chronic back or leg pain following lumbar discectomy (3), which is sometimes referred to as "failed back surgery syndrome" (FBSS) (75). The reported incidence of recurrent disc herniation varies between 1% and 27%, depending on herniation type, surgical technique, and duration of follow-up (74,76,77). In a prospective cohort study of patients undergoing first-time discectomy for radiculopathy, 10% experienced a symptomatic same-level recurrent LDH requiring reoperation (77). Greater annular defect area and having a lower proportion of disc volume removed are associated with greater risk of symptomatic recurrent disc herniation (74,76,77). Lumbar discectomy is also associated with higher rates of subsequent lumbar fusion, with population-level claims data showing that 8.5% of patients who receive a lumbar discectomy undergo lumbar fusion within 10 years of the discectomy. Individuals who had undergone a lumbar discectomy were almost 3 times more likely to receive lumbar fusion than those with a lumbar diagnosis who had not undergone a lumbar discectomy (78).

Tissue damage caused by the surgical procedure may increase spinal instability and/or accelerate disc degeneration, which may contribute to chronic pain (69). Discectomy is consistently associated with reductions in postoperative disc height (79,80), with one study showing over half of patients experiencing > 25% disc height loss within 2 years of surgery (77). Greater volume of disc removal is associated with accelerated disc height loss (77), suggesting a trade-off between limiting reherniation risk and maintaining disc height in determining the optimal amount of material to remove during discectomy (80). Discectomy is also associated with endplate degeneration as measured by Modic changes, which are changes in vertebral bone marrow signal intensity seen on T1- and T2-weighted magnetic resonance imaging (MRI) scans. In a small prospective study of patients who received a microdiscectomy, Modic type 2 or 3 endplate changes were twice as frequent at the 2-year follow-up as they were before surgery (79). Disc height loss and Modic changes have been proposed as potential pain generators based on observed correlations, although the mechanisms underlying these associations are not yet understood (79-81). Two meta-analyses have concluded that Modic changes do not significantly impact clinical outcomes after lumbar surgery (75,82). The clinical significance of disc height loss and Modic changes remains unclear.

Several preoperative prognostic factors for outcomes of lumbar discectomy have been identified. Notably, prolonged symptom duration is associated with worse outcomes. A post hoc analysis of the SPORT trial found that the persistence of symptoms for over 6 months was associated with worse outcomes in both surgical and nonsurgical groups (83). Corroborating the SPORT findings, 2 systematic reviews concluded that longer symptom duration negatively impacted discectomy outcomes, based on results from 6 to 9 studies (75,84). This association between shorter duration of symptoms and superior outcomes suggests that earlier, targeted interventions to decompress the nerve roots may improve outcomes for patients with LDH.

Preoperative predictors of positive post-discectomy outcomes include younger age, better mental health status (75), and a preponderance of radicular leg pain as opposed to back pain (85). Herniation type has also been shown to impact postsurgical outcomes. In a prospective study of a young, active population, patients with sequestered or extruded LDH had better pain and disability outcomes after receiving a discectomy than did those with contained LDH (85). Having an intact annulus fibrosis has also been associated with worse postoperative outcomes (75). Additionally, smoking is associated with a poorer post-discectomy prognosis, including a reduced rate of return to work/duty (75,85). While there is some conflicting evidence on the impact of obesity on postoperative clinical outcomes (75), obese patients who receive a discectomy appear to show similar treatment effects to those exhibited by nonobese patients (86,87). However, obese patients have longer operation times, greater intraoperative blood loss, and longer length of hospital stay than do nonobese patients (86). Recently, a meta-analysis found that receiving preoperative ESIs within one month of lumbar spine decompression surgery was associated with a 0.6% greater risk of postoperative infection (compared to that of patients who received no ESIs within one month) (88). Collectively, the evidence indicates that discectomy provides immediate relief from LDH, but these benefits must be considered against the risk of complications, potential long-term consequences, and declining effectiveness over time.

Other Treatments

Additional treatments are primarily used for disc degeneration and chronic low back pain, the latter of which has a more heterogeneous etiology than radicular leg pain. Spinal cord stimulation (SCS), also known as neuromodulation, is indicated for treatment-refractory chronic pain, including persistent spine pain syndrome (PSPS), previously failed back surgery syndrome (FBSS) and chronic neuropathic pain (89,90). SCS involves implanting a pulse generator device that sends electrical pulses to the spinal cord with the aim of interrupting pain signals to the brain. While SCS placement is associated with complications, such as infection, hardware malfunction, and lead migration, technological advances in miniaturization and battery-free implants are expected to address some of these issues (90).

Another strategy to disrupt the transmission of pain signals from the spinal cord to the brain involves applying radiofrequency energy to ablate the nerve thought to be the pain source. Intraosseous radiofrequency ablation of the basivertebral nerve has been shown to reduce disability more successfully than does sham control, with statistically significant improvements at 3-month (91) and 5-year follow-ups (92) in patients with chronic low back pain. Specifically, radiofrequency ablation of the basivertebral nerve is indicated for chronic (> 6 months) low back pain that has not responded to ≥ 6 months of conservative care and demonstrates Modic type 1 or type 2 changes on an MRI scan (93).

Regenerative medicine approaches, including platelet-rich plasma (PRP) and mesenchymal stem cell (MSC) injections, aim to repair spinal pathology with autologous or allogeneic biologics. While few RCTs have investigated the safety and efficacy of intradiscal regenerative therapies, PRP and/or stem cells are used in the treatment of spinal pain caused by LDH (67,94). The FDA has not approved any regenerative medicine products for the treatment of an orthopedic condition but has granted Regenerative Medicine Advanced Therapy (RMAT) designations to several investigational cell-based regenerative therapies, including rexlemestrocel-L (i.e., allogeneic mesenchymal precursor cells derived from human bone marrow) for chronic low back pain and injectable disc cell therapy (IDCT [rebonuputemcel], allogeneic discogenic progenitor cell therapy) for symptomatic lumbar degenerative disc disease. Other intradiscal injectates used for discogenic low back pain include fibrin and methylene blue (67).

Emerging Treatments

Several emerging therapies for radicular leg pain secondary to LDH are expected to improve the treatment landscape over the next few years, including novel ESI formulations and the resurgence of chemonucleolysis (Table 1). To mitigate safety concerns associated with particulate steroids, SP-102 was developed as a novel formulation of a soluble glucocorticoid, dexamethasone (10 mg), in an injectable viscous gel designed to extend residency time at the injection site (95). A phase 1/2 study (NCT03613662) demonstrated that SP-102 was well tolerated and that a repeat dose did not appear to have cumulative effects on HPA suppression (95). Recently, a phase 3 trial of SP-102 (NCT03372161) met its primary endpoint of improving average daily leg pain to a greater extent than did a placebo at 4 weeks post-injection in patients with lumbosacral radicular pain. SP-102 has been granted fast-track designation by the FDA and, if approved, would be the first corticosteroid approved for epidural injections. In Australia, another dexamethasone formulation designed for extended release via transforaminal ESI, SX600, completed a phase 1/2 clinical trial evaluating the proportion of patients who experienced a ≥ 50% improvement in mean worst daily leg pain 60 days after the injection (NCT03952377).

A promising approach for directly relieving LDH nerve root compression and its associated symptoms is chemonucleolysis, a nonsurgical method of dissolving the herniated disc material by injecting an enzyme into the disc. First described by Smith in 1964, chemonucleolysis was initially performed using the enzyme chymopapain, a non-specific protease derived from the papaya plant. Chymopapain showed a high success rate (82%) over a placebo in a randomized, double-blind study and was granted FDA approval in 1982 (96,97). Chymopapain was widely used in North America, Europe, Australia, and Korea to treat LDH effectively (97-99). The most serious adverse reaction to the enzyme was anaphylaxis, which occurred in approximately 0.5% of patients, and could be mitigated with prior testing for allergic sensitivity to papain (papaya) (97). A meta-analysis of RCTs concluded that there was strong evidence that chemonucleolysis with chymopapain was more effective than the placebo was, while discectomy was more effective than was chemonucleolysis with chymopapain (1). The manufacture of chymopapain was discontinued around 1999 (100), and thus chymopapain was withdrawn from the market for nonscientific commercial reasons (i.e., reasons other

Table 1. *Clinical trials for LDH and radicular symptoms.*

Agent	Condition	Proposed MOA	ROA	Status	Location	NCT ID
SP-102	Lumbosacral radicular pain	Extended-release dexamethasone (glucocorticoid)	Epidural injection	Phase 3 completed	US	NCT03372161
SX600	Radicular pain secondary to LDH	Extended-release dexamethasone (glucocorticoid)	Transforaminal epidural injection	Phase 1/2 completed	Australia	NCT03952377
SI-6603 (condoliase)	Radicular leg pain secondary to LDH	Enzyme degrades GAGs to reduce disc volume	Intradiscal injection	Phase 3 completed	US	NCT03607838
Oxygen-ozone	LDH	Oxygen-ozone reduces disc volume	Intradiscal injection	Not approved	Europe	NCT02525120
STA363	Radiculopathy due to LDH	Lactic acid reduces disc volume	Intradiscal injection	Phase 1b ongoing	Poland	NCT06022263
Gelified ethanol	Lumbar discogenic pain	Ethanol dehydration of NP to reduce disc volume	Intradiscal injection	Post-CE surveillance	France	NCT03415828
KLS-2031	Neuropathic pain from lumbosacral radiculopathy	Gene therapy	Transforaminal epidural injection	Phase 1/2 completed	US	NCT04238793

CE, Conformité Européenne; GAGs, glycosaminoglycans; LDH, lumbar disc herniation; MOA, mechanism of action; NP, nucleus pulposus; ROA, route of administration.

than safety and effectiveness) (99,101). Currently, no chemonucleolytic drug is approved in the US, leaving a gap in the treatment armamentarium.

In response to the need for a chemonucleolytic treatment, a phase 1b study (NCT06022263) is ongoing in Poland to evaluate the intradiscal injection of STA363 (lactic acid mixed with the contrast agent iohexol) for the treatment of LDH-caused radiculopathy. In a similar manner to chymopapain, STA363 is hypothesized to reduce disc volume in patients with moderately degenerated discs and disc intensity on T2-weighted MRI scans. The effect of lactate on glycosaminoglycans (GAGs) has been verified in rat nucleus pulposus cells (102), and the acidity of STA363 likely contributes to disc dehydration, since the synthesis of proteoglycans in human discs ex vivo is inhibited by low pH (103).

SI-6603 (condoliase), a novel chemonucleolytic and minimally invasive drug, was approved in Japan in 2018 and recently completed a US phase 3 trial (NCT03607838) in patients with LDH. As opposed to the nonspecific proteolytic activity of chymopapain, condoliase (chondroitin sulfate ABC endolyase) is a GAG-degrading enzyme isolated and purified from the gram-negative bacillus Proteus vulgaris (104). By specifically degrading the GAGs (particularly chondroitin sulfate) of proteoglycans abundant in the nucleus pulposus, condoliase is thought to reduce water retention in the nucleus pulposus, decreasing intradiscal pressure and nerve root compression, and thereby relieving pain while leaving surrounding tissues largely unaffected (105-107).

In phase 2/3 and phase 3 clinical trials in Japan, condoliase administration demonstrated a clinically significant improvement in leg pain over a placebo in patients with contained LDH (i.e., protrusion or subligamentous extrusion) who failed to improve after ≥6 weeks of conservative treatment prior to trial enrollment (106,108). In the Japanese phase 3 trial, clinically significant improvements emerged 2 weeks after condoliase injection and were sustained for the duration of the study, one year after condoliase administration. In addition, significant improvements associated with condoliase (over those associated with a placebo) were observed in worst back pain, disability (Oswestry Disability Index [ODI] score), the straight-leg raise (SLR) test, and quality of life measures (the physical component of the 36-Item Short Form Health Survey [SF-36]) (108). Condoliase was well tolerated in the Japanese phase 2/3 and phase 3 studies, with no instances of anaphylaxis, neurologic sequelae, or death (106,108). In a long-term follow-up study of the Japanese condoliase clinical trials, the one-year postinjection surgical intervention rates were 8.5% for the condoliase group and 16.7% for the placebo group, and the 6-year surgical intervention rates were 13.4% for the condoliase group and 20.7% for the placebo group (109).

Other chemonucleolytic therapies are in various stages of development, mostly outside of the US. One example is oxygen-ozone therapy, in which a mixture of oxygen and ozone gas is administered intradiscally with the aim of reducing the herniated disc volume. Ozone gas is highly unstable and generally requires caution for medical use. Using a novel oxygen-ozone generator system, a pilot, prospective, noninferiority RCT in Europe (NCT02525120) recently found that

oxygen-ozone injections were noninferior to microdiscectomy in improving radicular leg pain at a 6-month follow-up. Patients who received oxygen-ozone injections had faster procedure time and shorter discharge time than did those who received a discectomy, and 71% of patients who received oxygen-ozone therapy avoided a discectomy at the 6-month follow-up (110).

Another chemonucleolytic therapy, radiopaque gelified ethanol, was introduced to the European market in 2007 and re-obtained a Conformité Européenne (CE) mark in 2017. Gelified ethanol is believed to degrade the GAGs of the nucleus pulposus, resulting in dehydration and decompression of the disc. While some observational studies reported high success rates with gelified ethanol (111), especially when administered with intra-articular steroids (112), another small clinical study found high rates of treatment failure (113). A post-market clinical follow-up study comparing the effects of gelified ethanol to those of steroids on patients with lumbar discogenic pain is ongoing in France (NCT03415828).

In addition, a gene therapy to treat neuropathic pain caused by lumbosacral radiculopathy is in development. KLS-2031 is a combination gene therapy comprising recombinant adeno-associated viruses (AAVs) expressing glutamate decarboxylase 65 (GAD65), glial-cell-derived neurotrophic factor (GDNF), and interleukin-10 (IL-10), delivered by transforaminal injection to the dorsal root ganglion. This therapy has demonstrated analgesic effects in a rodent model of nerve injury (114). KLS-2031 has recently completed a first-in-human phase 1/2 clinical trial in patients with neuropathic pain from lumbosacral radiculopathy (NCT04238793) and been granted fast-track designation by the FDA.

Limitations

This review paper has several limitations. Inherent to narrative reviews, literature search and selection processes were not systematic in nature and may not have included all relevant literature on these topics. In addition, the evidence regarding the long-term efficacy of some treatments, such as discectomy, is limited by high rates of crossover between treatment groups

Conclusions

In the treatment armamentarium for persistent LDH, there is a gap between approaches focused on symptom relief, such as conservative care and ESIs, and more invasive surgical approaches that relieve the pressure on the spinal nerves. Although they have not received FDA approval, lumbar ESIs provide short-term pain relief but negligible long-term benefit. For patients with refractory LDH symptoms who are candidates for surgery, discectomy is effective in relieving pain in the short term, but the benefits appear to diminish over time. While the risk of surgical complications associated with lumbar EDIs is low, a substantial portion of patients who undergo these treatments experience recurrent pain, require revision surgery, and/or show spinal structural changes of unknown clinical significance. Prolonged LDH symptom duration alone is associated with worse outcomes, suggesting that prompt, longer-lasting treatment of persistent radicular pain may be beneficial. Emerging therapies with promising safety profiles and longer-term benefits may help close the gap in the LDH treatment landscape. Among emerging therapies that are in late-stage development, novel ESI formulations have the potential to offer patients another symptomatic treatment for LDH, while chemonucleolysis with condoliase could offer a minimally invasive alternative to discectomy that addresses the underlying LDH disease process. New minimally invasive treatment options, including those that address underlying disease pathophysiology, may improve outcomes for patients with LDH and address unmet therapeutic needs.

Acknowledgments

Medical writing support and publication assistance were provided by SCIENT Healthcare Communications.

Author Contributions

All authors contributed to the conception of the work and preparation of the manuscript. All authors have reviewed and approved the final manuscript and are accountable for the work.

Conflict of Interest

Medical writing support was funded by Ferring Pharmaceuticals, Inc. The academic authors did not receive compensation from Ferring for this work. DB has received grants or contracts from Medtronic, Medical Metrics, Avanos, Relievant, Boston Scientific, Stryker, Sollis Pharmaceuticals, Simplify Medical, Lenoss Medical, Spine BioPharma, Smart Soft, Tissue Tech, VIVEX, Stratus Medical, Restorative Therapies, Companion Spine, DiscGenics, SI Bone, and Choice Spine; royalties from VIVEX and IZI; consulting fees from Medtronic, ReGelTec, Nanofuse, Talosix, Spinal Simplicity, Pain Theory, Spark Biomedical, Smart Soft, Tissue Tech,

Bronx Medical, Thermaquil, VIVEX, Genesys, SetBone Medical, Amber Implants, Cerapedics, SpinaFX, and SI Bone; and travel support from Stryker, Medtronic, Boston Scientific, Merit, Avanos, Piramal, Genesys, and Elliquence. DB also has the following patents: Application No. 15/036,169, Issue Date 3/26/2019, and Patent No. 10238450, Attorney Document No 50950-00005, Confirmation No 5639. Additionally, DB has served on the National Institutes of Health (NIH) - National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) and NIAMS Observational Study Monitoring Board (OSMB)/Data and Safety Monitoring Board (DSMB) for the following 3 Mechanistic Research Center (MRC) studies within the NIH Back Pain Consortium (BACPAC) Research Program: University of Michigan BACPAC Mechanistic Research Center (1 U19 AR076734-01), UCSF Core Center for Patient-centric Mechanistic Phenotyping in Chronic Low Back Pain (1 U19 AR076737-01), and HEALing LB3P: Profiling Biomechanical, Biological and Behavioral Phenotypes (1 U19 AR076725-01); has served as the Safety Officer for National Institutes of Health (NIH) - NIAMS for Observational Study Monitoring Board (OSMB)/Data and Safety Monitoring Board (DSMB) for the Mechanistic Research Center (MRC) studies within the NIH Back Pain Consortium (BACPAC) Research Program; and has held a leadership or fiduciary role at Aclarion, VIVEX, Orthoson, and Choice Spine. KK has received grants or contracts made to his institution from Empirical Spine, Cerapedics, InVivo Therapeutics, Medtronic, Stryker, Seikagaku, and AbbVie; has received royalties from ZimVie and Precision Spine; has received consulting fees from Medtronic, Globus, Seikagaku, and ZimVie; has received payments or honoraria from ZimVie and GS Medical; has served as a member of the board of directors, receiving stock options, for Molecular Matrix; and has received payments for participating in an advisory board for InVivo Therapeutics. KM has received payment or honoraria as a speaker for Relievant Medsystems. KD, KC, MS, and AG are employees of Ferring Pharmaceuticals, Inc. AV has received royalties from Medtronic, Stryker Spine, Globus, Thieme, Jaypee, Elsevier, Taylor Francis/Hodder and Stoughton, Spinewave, Atlas Spine, and Atec; has received consulting fees from Spinal Elements; has served on committees for Sentryx, National Spine Health Foundations, and Accelus; and has stock in Globus, Stout Medical, Progressive Spinal Technologies, Advanced Spinal Intellectual Properties, Flagship Surgical, Cytonics, Electrocore, AVKN Patient Driven Care, FlowPharma, Rothman Institute and Related Properties, Innovative Surgical Design, Orthobullets, Avaz Surgical, Dimension Orthotics, Atlas Spine, Nuvasive, Parvizi Surgical Innovation, Jushi, Deep Health, ViewFi Health, Sentryx, Accelus, and Harvard Medtech.

References

1. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse. *Cochrane Database Syst Rev* 2007; 2007:CD001350.
2. Koes BW, van Tulder MW, Peul WC. Diagnosis and treatment of sciatica. *BMJ* 2007; 334:1313-1317.
3. Kreiner DS, Hwang SW, Easa JE, et al. An evidence-based clinical guideline for the diagnosis and treatment of lumbar disc herniation with radiculopathy. *Spine J* 2014; 14:180-191.
4. Rasouli MR, Rahimi-Movaghar V, Shokraneh F, Moradi-Lakeh M, Chou R. Minimally invasive discectomy versus microdiscectomy/open discectomy for symptomatic lumbar disc herniation. *Cochrane Database Syst Rev* 2014:CD010328.
5. Konstantinou K, Hider SL, Jordan JL, Lewis M, Dunn KM, Hay EM. The impact of low back-related leg pain on outcomes as compared with low back pain alone: A systematic review of the literature. *Clin J Pain* 2013; 29:644-654.
6. Hider SL, Whitehurst DG, Thomas E, Foster NE. Pain location matters: The impact of leg pain on health care use, work disability and quality of life in patients with low back pain. *Eur Spine J* 2015; 24:444-451.
7. Fardon DF, Williams AL, Dohring EJ, Murtagh FR, Rothman SLG, Sze GK. Lumbar disc nomenclature: Version 2.0: Recommendations of the combined task forces of the North American Spine Society, the American Society of Spine Radiology and the American Society of Neuroradiology. *Spine J* 2014; 14:2525-2545.
8. Jordan J, Konstantinou K, O'Dowd J. Herniated lumbar disc. *BMJ Clin Evid* 2009; 2009.
9. Manchikanti L, Knezevic NN, Navani A. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. *Pain Physician* 2021; 24:S27-S208.
10. Manchikanti L, Abdi S, Atluri S, et al. An update of comprehensive evidence-based guidelines for interventional techniques in chronic spinal pain. Part II: guidance and recommendations. *Pain Physician* 2013; 16:S49-283.
11. Weber H. Lumbar disc herniation. A controlled, prospective study with ten years of observation. *Spine (Phila Pa 1976)* 1983; 8:131-140.
12. Chou R, Atlas SJ, Stanos SP, Rosenquist RW. Nonsurgical interventional therapies for low back pain: A review of the evidence for an American Pain Society clinical practice guideline. *Spine (Phila Pa 1976)* 2009; 34:1078-1093.
13. Schoenfeld AJ, Weiner BK. Treatment of lumbar disc herniation: Evidence-based practice. *Int J Gen Med* 2010; 3:209-214.
14. Vroomen PC, de Krom MC, Wilmink JT, Kester AD, Knottnerus JT. Lack of

effectiveness of bed rest for sciatica. *N Engl J Med* 1999; 340:418-423.

15. Knezevic NN, Mandalia S, Raasch J, Knezevic I, Candido KD. Treatment of chronic low back pain - new approaches on the horizon. *J Pain Res* 2017; 10:1111-1123.
16. Stochkendahl MJ, Kjaer P, Hartvigsen J, et al. National Clinical Guidelines for non-surgical treatment of patients with recent onset low back pain or lumbar radiculopathy. *Eur Spine J* 2018; 27:60-75.
17. Pinto RZ, Verwoerd AJH, Koes BW. Which pain medications are effective for sciatica (radicular leg pain)? *BMJ* 2017; 359:j4248.
18. Rasmussen-Barr E, Held U, Grooten WJ, et al. Non-steroidal anti-inflammatory drugs for sciatica. *Cochrane Database Syst Rev* 2016; 10:CD012382.
19. American Society of Anesthesiologists Task Force on Chronic Pain Management; American Society of Regional Anesthesia and Pain Medicine. Practice guidelines for chronic pain management: An updated report by the American Society of Anesthesiologists Task Force on Chronic Pain Management and the American Society of Regional Anesthesia and Pain Medicine. *Anesthesiology* 2010; 112:810-833.
20. National Guideline Centre (UK). *Evidence Review for Pharmacological Management of Sciatica: Low Back Pain and Sciatica in Over 16s: Assessment and Msanagement.* London: National Institute for Health and Care Excellence; September 2020. NICE Guideline, No. 59.
21. Mathieson S, Maher CG, McLachlan AJ, et al. Trial of pregabalin for acute and chronic sciatica. *N Engl J Med* 2017; 376:1111-1120.
22. Evoy KE, Sadrameli S, Contreras J, Covvey JR, Peckham AM, Morrison MD. Abuse and misuse of pregabalin and gabapentin: A systematic review update. *Drugs* 2021; 81:125-156.
23. Boscarino JA, Rukstalis M, Hoffman SN, et al. Risk factors for drug dependence among out-patients on opioid therapy in a large US health-care system. *Addiction* 2010; 105:1776-1782.
24. Migliorini F, Vaishya R, Pappalardo G, Schneider M, Bell A, Maffulli N. Between guidelines and clinical trials: Evidence-based advice on the pharmacological management of non-specific chronic low back pain. *BMC Musculoskelet Disord* 2023; 24:432.
25. Neelamegam M, Zgibor J, Chen H, et al. The effect of opioids on the cognitive function of older adults: Results from the personality and total health through life Study. *Age Ageing* 2021; 50:1699-1708.
26. Hahne AJ, Ford JJ, McMeeken JM. Conservative management of lumbar disc herniation with associated radiculopathy: A systematic review. *Spine (Phila Pa 1976)* 2010; 35:E488-504.
27. Chou R, Loeser JD, Owens DK, et al; American Pain Society Low Back Pain Guideline Panel. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: An evidence-based clinical practice guideline from the American Pain Society. *Spine (Phila Pa 1976)* 2009; 34:1066-1077.
28. Manchikanti L, Pampati V, Falco FJ, Hirsch JA. Assessment of the growth of epidural injections in the Medicare population from 2000 to 2011. *Pain Physician* 2013; 16:E349-364.
29. Cohen SP, Greuber E, Vought K, Lissin D. Safety of epidural steroid injections for lumbosacral radicular pain: Unmet medical need. *Clin J Pain* 2021; 37:707-717.
30. Derby R, Lee SH, Date ES, Lee JH, Lee CH. Size and aggregation of corticosteroids used for epidural injections. *Pain Med* 2008; 9:227-234.
31. Centers for Disease Control and Prevention. Multistate outbreak of fungal infection associated with injection of methylprednisolone acetate solution from a single compounding pharmacy — United States, 2012. *MMWR Morb Mortal Wkly Rep* 2012; 61:839-842.
32. US Food and Drug Administration. FDA Drug Safety Communication: FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain. US Food and Drug Administration. 04/23/2014. Date updated 01/15/2016. Date accessed 02/29/2024. www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-requires-label-changes-warn-rare-serious-neurologic-problems-after.
33. US Food and Drug Administration. Anesthetic and Analgesic Drug Products Advisory Committee Meeting. Epidural steroid injections (ESI) and the risk of serious neurologic adverse reactions; 2014. https://scrip.citeline.com/-/media/pmbi-old-site/supporting-documents/the-pink-sheet-daily/2014/november/112114-fda-edpidural-adcom-background.pdf
34. Manchikanti L, Knezevic E, Latchaw RE, et al. Comparative systematic review and meta-analysis of Cochrane Review of epidural injections for lumbar radiculopathy or sciatica. *Pain Physician* 2022; 25:E889-E916.
35. Oliveira CB, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections for sciatica: An abridged Cochrane systematic review and meta-analysis. *Spine (Phila Pa 1976)* 2020; 45:E1405-E1415.
36. Lee JH, Kim DH, Kim DH, 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; 21:449-468.
37. Manchikanti L, Benyamin RM, Falco FJ, Kaye AD, Hirsch JA. Do epidural injections provide short- and long-term relief for lumbar disc herniation? A systematic review. *Clin Orthop Relat Res* 2015; 473:1940-1956.
38. Pinto RZ, Maher CG, Ferreira ML, et al. Epidural corticosteroid injections in the management of sciatica: A systematic review and meta-analysis. *Ann Intern Med* 2012; 157:865-877.
39. Bicket MC, Horowitz JM, Benzon HT, Cohen SP. Epidural injections in prevention of surgery for spinal pain: Systematic review and meta-analysis of randomized controlled trials. *Spine J* 2015; 15:348-362.
40. Kennedy DJ, Zheng PZ, Smuck M, McCormick ZL, Huynh L, Schneider BJ. A minimum of 5-year follow-up after lumbar transforaminal epidural steroid injections in patients with lumbar radicular pain due to intervertebral disc herniation. *Spine J* 2018; 18:29-35.
41. Koltsov JCB, Smuck MW, Zagel A, et al. Lumbar epidural steroid injections for herniation and stenosis: Incidence and risk factors of subsequent surgery. *Spine J* 2019; 19:199-205.
42. Murthy NS, Geske JR, Shelerud RA, et al. The effectiveness of repeat lumbar transforaminal epidural steroid injections. *Pain Med* 2014; 15:1686-1694.
43. Hynes JP, Fhlatharta MN, Ryan JW, MacMahon PJ, Eustace FJ, Kavanagh EC. Complications in image-guided musculoskeletal injections. *Skeletal Radiol* 2021; 50:343-349.
44. Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, Fellows B. A prospective evaluation of complications of 10,000 fluoroscopically directed

epidural injections. *Pain Physician* 2012; 15:131-140.

45. Rathmell JP, Benzon HT, Dreyfuss P, et al. Safeguards to prevent neurologic complications after epidural steroid injections: Consensus opinions from a multidisciplinary working group and national organizations. *Anesthesiology* 2015; 122:974-984.
46. Krez A, Liu Y, Kanbour S, Clare S, Waldman S, Stein EM. The skeletal consequences of epidural steroid injections: A literature review. *Osteoporos Int* 2021; 32:2155-2162.
47. Stout A, Friedly J, Standaert CJ. Systemic absorption and side effects of locally injected glucocorticoids. *PM R* 2019; 11:409-419.
48. Clare S, Dash A, Liu Y, et al. Epidural steroid injections acutely suppress bone formation markers in postmenopausal women. *J Clin Endocrinol Metab* 2022; 107:e3281-e3287.
49. Friedly JL, Comstock BA, Heagerty PJ, et al. Systemic effects of epidural steroid injections for spinal stenosis. *Pain* 2018; 159:876-883.
50. Singla A, Yang S, Werner BC, et al. The impact of preoperative epidural injections on postoperative infection in lumbar fusion surgery. *J Neurosurg Spine* 2017; 26:645-649.
51. Yang S, Werner BC, Cancienne JM, et al. Preoperative epidural injections are associated with increased risk of infection after single-level lumbar decompression. *Spine J* 2016; 16:191-196.
52. Even JL, Crosby CG, Song Y, McGirt MJ, Devin CJ. Effects of epidural steroid injections on blood glucose levels in patients with diabetes mellitus. *Spine (Phila Pa 1976)* 2012; 37:E46-50.
53. Briot K, Roux C. Glucocorticoid-induced osteoporosis. *RMD Open* 2015; 1:e000014.
54. Mandel S, Schilling J, Peterson E, Rao DS, Sanders W. A retrospective analysis of vertebral body fractures following epidural steroid injections. *J Bone Joint Surg Am* 2013; 95:961-964.
55. Stecker MS, Balter S, Towbin RB, et al. Guidelines for patient radiation dose management. *J Vasc Interv Radiol* 2009; 20:S263-S273.
56. Hwang YM, Lee MH, Kim SJ, et al. Comparison of radiation exposure during fluoroscopy-guided transforaminal epidural steroid injections at different vertebral levels. *Korean J Radiol* 2015; 16:357-362.
57. Gibson JN, Waddell G. Surgical interventions for lumbar disc prolapse: Updated Cochrane Review. *Spine (Phila Pa 1976)* 2007; 32:1735-1747.
58. Liu C, Ferreira GE, Abdel Shaheed C, et al. Surgical versus non-surgical treatment for sciatica: Systematic review and meta-analysis of randomised controlled trials. *BMJ* 2023; 381:e070730.
59. Peul WC, van den Hout WB, Brand R, Thomeer RTWM, Koes BW; Leiden-The Hague Spine Intervention Prognostic Study Group. Prolonged conservative care versus early surgery in patients with sciatica caused by lumbar disc herniation: Two-year results of a randomised controlled trial. *BMJ* 2008; 336:1355-1358.
60. Ahn UM, Ahn NU, Buchowski JM, Garrett ES, Sieber AN, Kostuik JP. Cauda equina syndrome secondary to lumbar disc herniation: A meta-analysis of surgical outcomes. *Spine (Phila Pa 1976)* 2000; 25:1515-1522.
61. Masuda S, Kanba Y, Kawai J, Ikeda N. Prognostic factors for drop foot due to lumbar degenerative diseases: The impact of surgical timing on postoperative recovery. *Clin Spine Surg* 2020; 33:160-162.
62. Osterman H, Seitsalo S, Karppinen J, Malmivaara A. Effectiveness of microdiscectomy for lumbar disc herniation: A randomized controlled trial with 2 years of follow-up. *Spine (Phila Pa 1976)* 2006; 31:2409-2414.
63. Peul WC, van Houwelingen HC, van den Hout WB, et al; Leiden-The Hague Spine Intervention Prognostic Study Group. Surgery versus prolonged conservative treatment for sciatica. *N Engl J Med* 2007; 356:2245-2256.
64. Oster BA, Kikanloo SR, Levine NL, Lian J, Cho W. Systematic review of outcomes following 10-year mark of Spine Patient Outcomes Research Trial (SPORT) for spinal stenosis. *Spine (Phila Pa 1976)* 2020; 45:832-836.
65. Bailey CS, Rasoulinejad P, Taylor D, et al. Surgery versus conservative care for persistent sciatica lasting 4 to 12 months. *N Engl J Med* 2020; 382:1093-1102.
66. Lurie JD, Tosteson TD, Tosteson AN, et al. Surgical versus nonoperative treatment for lumbar disc herniation: Eight-year results for the spine patient outcomes research trial. *Spine (Phila Pa 1976)* 2014; 39:3-16.
67. Sayed D, Grider J, Strand N, et al. The American Society of Pain and Neuroscience (ASPN) Evidence-Based Clinical Guideline of Interventional Treatments for low back pain. *J Pain Res* 2022; 15:3729-3832.
68. Birkenmaier C, Komp M, Leu HF, Wegener B, Reutten S. The current state of endoscopic disc surgery: Review of controlled studies comparing full-endoscopic procedures for disc herniations to standard procedures. *Pain Physician* 2013; 16:335-344.
69. Overdevest GM, Peul WC, Brand R, et al; Leiden-The Hague Spine Intervention Prognostic Study Group. Tubular discectomy versus conventional microdiscectomy for the treatment of lumbar disc herniation: Long-term results of a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2017; 88:1008-1016.
70. Ruetten S, Komp M, Merk H, Godolias G. Full-endoscopic interlaminar and transforaminal lumbar discectomy versus conventional microsurgical technique: A prospective, randomized, controlled study. *Spine (Phila Pa 1976)* 2008; 33:931-939.
71. Gadjradj PS, Harhangi BS, Amelink J, et al. Percutaneous transforaminal endoscopic discectomy versus open microdiscectomy for lumbar disc herniation: A systematic review and meta-analysis. *Spine (Phila Pa 1976)* 2021; 46:538-549.
72. Shriver MF, Xie JJ, Tye EY, et al. Lumbar microdiscectomy complication rates: A systematic review and meta-analysis. *Neurosurg Focus* 2015; 39:E6.
73. Chen X, Chamoli U, Vargas Castillo J, Ramakrishna VAS, Diwan AD. Complication rates of different discectomy techniques for symptomatic lumbar disc herniation: A systematic review and meta-analysis. *Eur Spine J* 2020; 29:1752-1770.
74. Harper R, Klineberg E. The evidence-based approach for surgical complications in the treatment of lumbar disc herniation. *Int Orthop* 2019; 43:975-980.
75. Wilson CA, Roffey DM, Chow D, Alkherayf F, Wai EK. A systematic review of preoperative predictors for postoperative clinical outcomes following lumbar discectomy. *Spine J* 2016; 16:1413-1422.
76. Carragee EJ, Spinnickie AO, Alamin TF, Paragioudakis S. A prospective controlled study of limited versus subtotal posterior discectomy: Short-term outcomes in patients with herniated lumbar intervertebral discs and large posterior anular defect. *Spine (Phila Pa 1976)* 2006; 31:653-657.

77. McGirt MJ, Eustacchio S, Varga P, et al. A prospective cohort study of close interval computed tomography and magnetic resonance imaging after primary lumbar discectomy: Factors associated with recurrent disc herniation and disc height loss. *Spine (Phila Pa 1976)* 2009; 34:2044-2051.
78. Castillo H, Chintapalli RTV, Boyajian HH, et al. Lumbar discectomy is associated with higher rates of lumbar fusion. *Spine J* 2019; 19:487-492.
79. Barth M, Diepers M, Weiss C, Thomés C. Two-year outcome after lumbar microdiscectomy versus microscopic sequestrectomy: Part 2: Radiographic evaluation and correlation with clinical outcome. *Spine (Phila Pa 1976)* 2008; 33:273-279.
80. Kursumovic A, Muir JM, Ammerman J, Bostelmann R. The disability cascade: A preventable consequence of the loss of disc height following lumbar microdiscectomy. *Cureus* 2019; 11:e5169.
81. Apfel CC, Cakmakkaya OS, Martin W, et al. Restoration of disk height through non-surgical spinal decompression is associated with decreased discogenic low back pain: A retrospective cohort study. *BMC Musculoskelet Disord* 2010; 11:155.
82. Lambrechts MJ, Brush P, Issa TZ, et al. Evaluating the impact of modic changes on operative treatment in the cervical and lumbar spine: A systematic review and meta-analysis. *Int J Environ Res Public Health* 2022; 19:10158.
83. Rihn JA, Hilibrand AS, Radcliff K, et al. Duration of symptoms resulting from lumbar disc herniation: Effect on treatment outcomes: Analysis of the Spine Patient Outcomes Research Trial (SPORT). *J Bone Joint Surg Am* 2011; 93:1906-1914.
84. Schoenfeld AJ, Bono CM. Does surgical timing influence functional recovery after lumbar discectomy? A systematic review. *Clin Orthop Relat Res* 2015; 473:1963-1970.
85. Dewing CB, Provencher MT, Riffenburgh RH, Kerr S, Manos RE. The outcomes of lumbar microdiscectomy in a young, active population: Correlation by herniation type and level. *Spine (Phila Pa 1976)* 2008; 33:33-38.
86. Rihn JA, Kurd M, Hilibrand AS, et al. The influence of obesity on the outcome of treatment of lumbar disc herniation: Analysis of the Spine Patient Outcomes Research Trial (SPORT). *J Bone Joint Surg Am* 2013; 95:1-8.
87. Rommelman M, Safdar A, Motiei-Langroudi R. Effect of obesity on surgical outcomes of lumbar microdiscectomy: A retrospective analysis of 525 patients. *Cureus* 2023; 15:e39719.
88. Hooten WM, Eberhart ND, Cao F, et al. Preoperative epidural steroid injections and postoperative infections after lumbar or cervical spine surgery: A systematic review and meta-analysis. *Mayo Clin Proc Innov Qual Outcomes* 2023; 7:349-365.
89. Lo Bianco G, Tinnirello A, Papa A, et al. Interventional pain procedures: A narrative review focusing on safety and complications. PART 2 Interventional proceduresfFor back pain. *J Pain Res* 2023:16: 761-772.
90. Strand N, J M, Tieppo Francio V, et al. Advances in pain medicine: A review of new technologies. *Curr Pain Headache Rep* 2022; 26:605-616.
91. Fischgrund JS, Rhyne A, Franke J, et al. Intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: A prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J* 2018; 27:1146-1156.
92. Fischgrund JS, Rhyne A, Macadaeg K, et al. Long-term outcomes following intraosseous basivertebral nerve ablation for the treatment of chronic low back pain: 5-year treatment arm results from a prospective randomized double-blind sham-controlled multi-center study. *Eur Spine J* 2020; 29:1925-1934.
93. Intracept Intraosseous Nerve Ablation System (RF Probe), Intracept Intraosseous Nerve Ablation System (Access Instruments), Relievant RF Generator. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf19/K190504.pdf. Accessed December 8, 2023.
94. Navani A, Manchikanti L, Albers SL, 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.
95. Radnovich R, Heinz J, Ambrose C, Stannard E, Lissin D. Repeat epidural injections of SP-102 (dexamethasone sodium phosphate injectable gel) in subjects with lumbosacral radiculopathy. *J Pain Res* 2021; 14:1231-1239.
96. Javid MJ, Nordby EJ, Ford LT, et al. Safety and efficacy of chymopapain (Chymodiactin) in herniated nucleus pulposus with sciatica. Results of a randomized, double-blind study. *JAMA* 1983; 249:2489-2494.
97. Simmons JW, Nordby EJ, Hadjipavlou AG. Chemonucleolysis: The state of the art. *Eur Spine J* 2001; 10:192-202.
98. Kim YS, Chin DK, Yoon DH, Jin BH, Cho YE. Predictors of successful outcome for lumbar chemonucleolysis: Analysis of 3000 cases during the past 14 years. *Neurosurgery* 2002; 51:S123-128.
99. Wardlaw D. Sciatica caused by disc herniation: Why is chymopapain chemonucleolysis denied to our patients? *Int J Spine Surg* 2016; 10:44.
100. Simmons JW, Fraser R. The rise and fall of chemonucleolysis. In: Kambin P (ed). *Arthroscopic and Endoscopic Spinal Surgery*. Humana Press, 2005, pp 351-358.