Sciatica: a review of history, epidemiology, pathogenesis, and the role of epidural steroid injection in management

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Radicular pain in the distribution of the sciatic nerve, resulting from herniation of one or more lumbar intervertebral discs, is a frequent and often debilitating event. The lifetime incidence of this condition is estimated to be between 13% and 40%. Fortunately, the majority of cases resolve spontaneously with simple analgesia and physiotherapy. However, the condition has the potential to become chronic and intractable, with major socio-economic implications. This review discusses the history, epidemiology, pathophysiology, and natural history of sciatica. A Medline search was performed to obtain the published literature on the sciatica, between 1966 and 2006. Hand searches of relevant journals were also performed. Epidemiological factors found to influence incidence of sciatica included increasing height, age, genetic predisposition, walking, jogging (if a previous history of sciatica), and particular physical occupations, including driving. The influence of herniated nucleus pulposus and the probable cytokine-mediated inflammatory response in lumbar and sacral nerve roots is discussed. An abnormal immune response and possible mechanical factors are also proposed as factors that may mediate pain. The ongoing issue of the role of epidural steroid injection in the treatment of this condition is also discussed, as well as potential hazards of this procedure and the direction that future research should take.


Keywords: analgesic techniques, epidural; analgesics anti-inflammatory, steroid; pain, neuropathic; pain, pathological; spinal cord, vertebral space

Sciatic neuralgia is defined as ‘pain in the distribution of the sciatic nerve due to pathology of the nerve itself’. Radicular pain is defined as ‘pain perceived as arising in a limb or the trunk caused by ectopic activation of nociceptive afferent fibres in a spinal nerve or its roots or other neuropathic mechanisms’. According to these definitions, sciatic neuralgia is clearly a form of radicular pain, and is described as a disease of the peripheral nervous system. The term ‘sciatica’ may cause confusion as it has been used to describe any pain, including referred, felt in the leg along the distribution of the sciatic nerve. Indeed, the term has been described as ‘an anachronism and should be abandoned’. Nevertheless, the term ‘sciatica’ remains in common usage both in clinical practice and in publications. Indeed, a Medline search from 1996 to 2006 reveals 1204 papers using ‘sciatica’ as a key word. The use of the term sciatica, however, should only be in the context of the above definitions and as such, be distinguished from any or all other forms of pain felt in the leg, particularly referred pain.

Sciatica is a relatively common condition with a lifetime incidence varying from 13% to 40%. The corresponding annual incidence of an episode of sciatica ranges from 1% to 5%. This review assesses current knowledge of the epidemiology, pathogenesis, and natural history of sciatica. The ongoing debate about the role of epidural steroid injection in the management of this condition is also discussed. Although this is a fairly safe procedure where hazards are usually mild and transient, serious complications can occur and so the patients should be fully aware of the balance between risk and benefit before giving informed consent. Despite a large number of clinical trials of epidural steroid injections for sciatica, the most important question remains unanswered, and indeed, unasked. Is the effect of epidural steroid injection due to a direct action on lumbar nerve roots or simply due to systemic uptake from the vascular epidural space?
Historical aspects

The ancient Greeks were familiar with sciatic neuralgia and used the term ‘sciatica’, to describe pains or ‘ischias’ felt around the hip or thigh. Hippocrates himself referred to ‘ischiatric’ pain affecting men between 40 and 60 yr. He observed that young men described pain that lasted about 40 days before resolving spontaneously. He also noted that pain radiating to the foot was a good prognostic sign, whereas localized hip pain was less likely to resolve.51

The Italian anatomist Domenico Cotugno (1736–1822) wrote the first book on sciatica in 1764 and for many years it was known as Cotugno’s disease.36 He was the first to distinguish sciatica due to nervous disease from the aching pain associated with low back pain. He observed that sciatica could be continuous or intermittent and noted that continuous pain could become intermittent, but not vice versa.

By the 19th century, sciatica was thought to be due to a variety of rheumatic conditions causing inflammation of the sciatic nerve. However, early frustrations with difficulties in identifying a cause of and treating sciatica were expressed by Fuller in his book Rheumatism, Rheumatic Gout and Sciatica (1852). He stated ‘the history of sciatica is, it must be confessed, the record of pathological ignorance and therapeutic failure’.37 There may be many pain management physicians who would agree with those sentiments today.

The intervertebral disc was first implicated as a causative factor in sciatica in the early 20th century. Schmorl94 and Andrae (1929)3 described posterior disc protrusions seen at post-mortem studies, but did not link these with sciatic pain and concluded they were probably asymptomatic in life. In an early surgical management of sciatica, the neurosurgeon Eslberg (1931)33 described removal of cartilaginous ‘tumours’ from the spinal canal, with subsequent improvement of symptoms. He considered the possibility that these ‘tumours’ could in fact be prolapsed disc material. This idea, however, was initially rejected.

The concept of prolapsed disc material causing pain was later revisited by Mixter and Barr who reviewed the pathology of all excised chondromas of the spine held in the Harvard Medical School pathology museum, comparing them with normal disc material. Of 16 specimens reviewed, 10 were judged to contain normal disc material. They concluded that sciatica and neurological sequelae were due to protrusion of normal disc material. Six months later, the first patient with a preoperative diagnosis of ‘ruptured intervertebral disc’ was operated on in the Massachusetts General Hospital. This led to the landmark paper published in the New England Journal of Medicine74 and since then, the prolapsed intervertebral disc has been irreversibly linked with the pathogenesis of sciatica.

The presence of pain was initially ascribed to pressure on nerve roots. This idea was challenged by Kelly,59 who felt that pressure on a nerve would lead to loss of function rather than pain; therefore, pain must arise by a different mechanism. Around the same time, Lindahl and Rexed64 found evidence of an inflammatory response on lumbar nerve roots at laminectomy leading to the theory that prolapse of an intervertebral disc may provoke an inflammatory reaction in lumbar nerve roots, causing the sciatic type pain. This theory led to an active research programme that is still ongoing.27

Epidemiology

A number of environmental and inherent factors thought to influence the development of sciatica have been studied, including gender, body habitus, parity, age, genetic factors, occupation, and environmental factors (Table 1).

A cross-sectional study of 2946 women and 2727 men showed neither gender nor body mass had an influence on the development of sciatica, although body mass may have been associated with low back pain.46 Body height may be a risk factor for sciatica, although this appears to be significant only in males in the 50–64 yr age group. Parity of up to six also has been identified as having no association with sciatica.46–48 The incidence of sciatica is related to age. Rarely seen before the age of 20, incidence peaks in the fifth decade and declines thereafter.35 This age distribution was also observed in those presenting for lumbar disc herniation surgery.98 The odds ratio (OR) of an episode of sciatica increased by 1.4 for every additional 10 yr of age, up to the age of 64.46 Interestingly, the site of disc herniation appears to change with age. Although the majority of disc herniations occur at the L4/5 or L5/S1 level, with advancing age, there appears to be a relatively increased incidence of herniation at the L3/4 or even L2/3 level.36

A genetic link with sciatica was first reported in a juvenile population.108 This has also been observed in the adult population, where both retro- and prospective observational studies identified a higher incidence of sciatica or prolapsed disc among first-degree relatives than controls in a population of patients presenting for surgery on herniated lumbar discs.69 96 A study of 9365 pairs of adult twins identified the lifetime incidence of sciatica in

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<th>Table 1</th>
<th>Factors associated with development of sciatica</th>
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<td><strong>Positive influence</strong></td>
<td>Increasing height (older age groups only)</td>
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Positive influence:
- Increasing height (older age groups only)
- Age
- Genetic pre-disposition
- Walking
- Jogging (pre-disposes to pain if previous history exists)
- Occupation (particularly if associated with physical activity, especially flexion/torsion of trunk, arms frequently raised above shoulder height, driving of motor vehicles)
- Smoking

No influence:
- Gender, body mass, parity
- Smoking
- Jogging (if no baseline history of sciatica)
monzygotic and dizygotic twins as 17.7% and 12%, respectively. The estimated heritability was 20.8% for those reporting sciatica and 10.6% for those admitted to hospital with sciatica.

Recreational activities, such as walking and jogging, may influence incidence of sciatica. Regular walking was shown to almost double the incidence of sciatica in a group of 2077 workers who were pain free at baseline. This study also showed that jogging had a dual effect on the incidence of sciatica. Although joggers who were pain free at baseline had a decreased incidence of sciatica, those with a previous history of sciatica were more likely to experience more episodes.

Physical activity associated with occupation has also been shown to influence incidence of sciatica. Carpenters (OR 1.7) and machine operators (OR 1.6) were shown to be more likely to develop sciatica than sedentary office workers. Retired (OR 0.15) or part-time (OR 0.16) farmers were less likely to develop sciatica than full-time ones. Risk factors identified for sciatica associated with occupation included awkward working position, working in a flexed or twisted trunk position (OR 2.6), or with the hand above the shoulder. Driving is also positively associated with sciatica or lumbar disc herniation. It is possible that driving causes exposure to vibration at around 4–5 Hz which may coincide with resonant frequency of the spine in the seated position and so leading to a direct mechanical effect on the lumbar disc.

Smoking has been linked with sciatica and several hypotheses, such as tobacco disturbing the metabolic balance of intervertebral discs, coughing causing marked elevations of intra-disc pressures, or a possible fibrinolytic effect of tobacco, have been proposed. An analysis of eight studies of smoking and sciatica revealed a positive correlation in only four of eight studies in men and one of five studies in women. Although there was a weak association between smoking and sciatica, these studies were cross-sectional and it was impossible to say that smoking preceded the sciatica.

Pathophysiology

The intervertebral disc was implicated in the pathophysiology of sciatica and with the assumption that the protruding disc exerted pressure on sciatic nerve roots, the treatment was surgical removal of the disc. Any subsequent improvement in symptoms was attributed to relief of pressure on the nerve roots. Kelly, however, suggested that pressure on a nerve results in loss of function and is rarely associated with pain. There are several lines of evidence to support this. Disc pathology and stenosis with apparent neural compromise have been shown to be a relatively common finding in asymptomatic patients. Symptomatic patients with disc herniation may experience marked improvement in symptoms without any alteration of the original pathology, whereas the removal of herniated disc material or other causes of nerve root compression does not always relieve pain.

A positive correlation was noted between contact pressure and preoperative neurological impairment, suggesting that pressure led to loss of function rather than pain, whereas chymopapain, a substance used for chemonucleolysis of herniated lumbar discs, may cause a rapid relief of leg pain that precedes any change in the size of the disc herniation or degree of nerve root impingement.

These observations suggest that processes other than pressure on nerve roots are involved in the development of sciatic neuralgia. The evidence suggests that a complex interplay of inflammatory, immunological, and pressure-related processes may be involved.

Inflammation

When Lindahl and Rexed found histological evidence of inflammation in posterior nerve roots examined during laminectomy, they postulated that inflammation rather than pressure was the source of nerve root pain. Support for this theory was provided when injection of autologous nucleus pulposus into canine epidural space provoked an intense inflammatory reaction involving the dura and nerve roots, with signs of epidural fibrosis present from as early as 2 weeks. High levels of phospholipase A2 (PLA2), an important enzyme in the inflammatory process, were demonstrated in herniated nuclear material of patients with radicular pain, whereas PLA2 isolated from human disc material was demonstrated to provoke an intense inflammatory reaction. PLA2 activity was noted to be higher in cases of sequestrated rather than bulging discs at the time of surgery, with a strong correlation between disc and plasma PLA2 levels.

Injection of PLA2 into rat epidural space caused motor weakness and altered sensation of the hind limbs, and sustained ectopic discharge of lumbar dorsal roots was provoked. Histological examination of nerve roots after 3 days revealed evidence of demyelination. Chymopapain, used for chemonucleolysis of herniated intervertebral discs, has anti-inflammatory properties, reducing PLA2 activity around inflamed sciatic nerves. This may explain why pain relief often precedes shrinkage of the herniated disc. Finally, PLA2 acting on cell membrane, releases arachidonic acid, a precursor of the inflammatory mediators leukotrienes, and thromboxanes (Fig. 1). Elevated levels of leukotriene B4 and thromboxane B2 have been demonstrated in human lumbar discs removed for relief of radicular pain.

Further evidence for the inflammatory properties of nucleus pulposus was demonstrated by s.c. injection of autologous disc material in pigs. Titanium chambers containing autologous nucleus pulposus material attracted significantly more leucocytes than those containing fat or empty ‘sham’ chambers. The injection of nucleus pulposus suspension also induced increased microvascular...
thrombosis and macromolecular leakage in hamster cheek pouch. Autologous nucleus pulposus applied to rat L5 nerve roots reduced blood flow to the dorsal root ganglion by up to 20%. This was a statistically significant reduction compared with controls. Endoneurial fluid pressure of the L5 nerve roots was also significantly raised compared with controls.115

Cytokines have also been implicated in the genesis of this inflammatory response. Analysis of homogenates of 77 discs removed from patients with nerve root pain revealed the presence of the cytokines interleukin-1α (IL-1α), IL-1β, IL-6, and tumour necrosis factor-α (TNF-α).103 High levels of IL-6, IL-8, and prostaglandin E2 (PGE2) were found in discs removed from patients having surgery for sciatica and low back pain.21 Raised levels of IL-8 in preoperative samples of cerebrospinal fluid (CSF) and serum in patients undergoing discectomy, correlated with a more pronounced degree of disc herniation noted at surgery.17

Cytokines, particularly TNF, induce synthesis of nitric oxide (NO), a potent mediator of inflammation. Raised NO synthase activity was detected in rat nerve roots exposed to autologous nucleus pulposus, whereas aminoguanidine, an NO synthase inhibitor, reduced the oedema and adverse effects on nerve conduction in pig nerve roots after exposure to nucleus pulposus.16

TNF-α appears to be the cytokine most strongly associated with the inflammatory properties of nucleus pulposus. This has been demonstrated to be present in pig nucleus pulposus, although the adverse effects of nucleus pulposus on nerve conduction were completely blocked by doxycycline, a compound that inhibits the effects of TNF-α.77

The effects on porcine sacrococcygeal cauda equina were inhibited by the selective TNF-α inhibitors etanercept and infliximab. These drugs reduced effects on nerve conduction velocity, intracapillary thrombus formation, and intraneural oedema formation compared with enoxaparin and control.79 Monoclonal anti-TNF-α antibodies were shown to inhibit the enhanced activity that was seen in wide dynamic range neurons of the superficial dorsal horn when autologous nucleus pulposus was applied to the L5 nerve root.50 Finally, infusion of the monoclonal anti-TNF-α antibody infliximab in 10 patients with herniated disc-induced sciatica led to significant reductions in pain levels at 1 h, 2 weeks, and 3 months, compared with historical controls.55 These studies all suggest that TNF-α plays an early and prominent role in the pathophysiological events that lead to nerve dysfunction and pain when nucleus pulposus is approximated to lumbar nerve roots.

Immunological

There is some evidence to suggest that the immune system also may play a part in the reaction between the nerve root and the exposed nucleus pulposus. Glycosphingolipids (GSLs) are particularly abundant in cell types of the central and peripheral nervous system.100 102 Titres of antibodies to these cell components are normally very low but become elevated in auto-immune conditions of the nervous system such as Guillain–Barré syndrome.7 Antibodies to GSLs were measured in patients with acute and chronic sciatica and those who had lumbar discectomy for disc herniation. Raised antibody levels to GSLs were
detected in 71% of patients with acute sciatica, 61% at 4 yr follow-up, and 54% of those undergoing discectomy.15

Markers of glial cell and nerve damage [neurofilament (NFL), glial fibrillary acidic protein, S-100 protein, and neuron-specific enolase] were measured in the CSF of patients presenting for lumbar disc surgery and compared with controls. CSF levels of NFL protein and S-100 were significantly elevated in patients appearing for disc surgery compared with controls. Patients with symptoms of sciatica for <3 months duration had higher NFL protein levels than those with symptoms for longer. Patients with persistent neurological findings at 3 months post-surgery had higher preoperative NFL levels than those who did not develop sequelae.18 These studies suggest that an immune reaction to nervous tissue may be involved in the pathogenesis of both acute and chronic sciatica.

Mechanical compression

The evidence above strongly suggests that an inflammatory and immune response is involved in the pathogenesis of nerve root irritation and sciatic type pain. There is also some evidence to suggest that nerve root compression may also be involved. Cauda equina compression with a non-irritant silicone tube in rats led to significantly higher rates of sural nerve ectopic firing than control animals. Administration of a nitroprusside infusion, a source of NO, led to increased ectopic firing only in those animals with cauda equina compression.81

An observational study, with magnetic resonance imaging (MRI) in 394 consecutive patients with leg pain, noted that 9.6% had no disc disease, 3.3% bulging, 11.4% protrusion, 68.5% extrusion, and 7.1% disc sequestration, respectively. A statistically significant positive correlation between the severity of disc disease and leg pain, and Roland-Morris and Prolo disability scales were observed, that is, those with larger herniations had more leg (but not back) pain and disability.85 Another observational study noted the prevalence of swelling of dorsal root ganglia and impingement within the intervertebral foramina at the appropriate level and side in patients with a unilateral monoradiculopathy. Again, the degree of swelling and impingement correlated well with severity of leg pain.4

As already noted, elevated CSF levels of NFL and S-100 were observed in patients with verified disc herniations. These proteins are nervous system specific and their presence indicates damage to central nervous system structures.18 When either an amnioid constrictor or an autologous nucleus pulposus material was applied to porcine S1 nerve root, it was noted only compression of the S1 nerve root significantly raised levels of NFL and total protein concentrations in the CSF. This was not seen with nucleus pulposus alone.97

Another animal model, exposing rats to experimental disc herniation, medial displacement of the fourth dorsal root ganglion, both or sham procedure revealed that exposure to nucleus pulposus without nerve root compression or chronic nerve root displacement alone did not significantly alter mechanical or thermal stimulatory thresholds. However, in animals exposed to both nucleus pulposus and nerve root displacement, there was a significant reduction in threshold for thermal stimuli that lasted for the 14 day experimental period.78 Histological examination of nerve roots revealed oedema in both nucleus pulposus exposed and displaced nerve roots, being slightly more severe in the displaced group. In animals exposed to both, histology of nerve roots indicated significant cellular injury at day 21, with oedema, fibrotic reactions, evidence of axonal demyelination, and Schwann cell hypertrophy.

From the above evidence, it could be proposed that radical pain in sciatic nerve roots arises from a complex interaction of inflammatory, immune, and pressure-related elements. This can most easily be appreciated in terms of intervertebral disc-mediated pain where the majority of research has been conducted, although it is probably equally applicable to all other forms of sciatic neuralgia. The high incidence of asymptomatic individuals with disc abnormalities associated with neural compromise shows that pressure alone does not cause pain in sciatic nerve roots. Although disc bulging, to a varying degree is common, nucleus pulposus sequestration or extrusion is rarely seen in asymptomatic individuals. The potent inflammatory properties of nucleus pulposus have been outlined earlier and involve the major inflammatory mediators. This causes an inflammatory reaction in sciatic nerve roots which has been shown, in animal models, to lead to sustained ectopic discharge, demyelination,28 decreased blood flow to the dorsal root ganglion, increased endoneurial pressure, and decreased conduction velocity.17 An inflammatory reaction normally leads to an immune response, but the above evidence suggests that an abnormal response may occur, with antibodies being formed to normal neural elements. Crucially, this may also be related to the development of chronic sciatica.

This inflammatory process seems to be exacerbated by the effects of nerve root pressure. Lumbo-sacral nerve roots, possibly due to the vulnerability of its venous drainage system, seem to be particularly susceptible to the effects of pressure. This may explain why even minor compression may lead to nerve root oedema, intraneural inflammation, and hypersensitivity.90 This theory is supported by Haddox, who wrote that ‘Surgeons ... state that the nerve root that is causing the problem is easily identifiable by its edematous inflammatory character’.43

Although passive congestion does not necessarily cause inflammation, this underlines the potential for lumbar nerve roots to become congested and swollen which presumably exacerbates any underlying inflammation. This combination of susceptibility to inflammation and pressure effects with subsequent oedema may be what makes the lumbo-sacral nerve roots so particularly vulnerable to neuropathies.
Other causes of sciatica

Impingement of the intervertebral disc on lumbar nerve roots is a frequent but by no means the only cause of sciatica. Any new presentation with pain in a nerve root distribution, or change in a previously stable pain state, should be carefully investigated to exclude infective or malignant causes of pain. Malignancy causing compression along the extra-sciapinal course of the sciatic nerve was noted in 32 cases of sciatica, which was constant, progressive, and unresponsive to bed rest.9 Eighteen of the cases were due to malignant tumours (six, metastatic; five, primary bone sarcoma; and seven, soft tissue sarcoma). Two were tumours of the sciatic nerve itself. Other rare malignant causes of sciatica include haemangioblastoma on a sacral root50 and lung adenocarcinoma metastasis in the pelvis (Table 2).105 These underline the importance of appropriate investigation of all new cases of sciatica.

Infection also needs to be excluded in cases of sciatica. A Staphylococcus aureus epidural abscess was reported to cause sciatica.66 Caseating tuberculosis has been associated with sciatica.27 113 Chronic infection of the lower lumbar intervertebral discs themselves with Propionibacterium acnes has also been implicated in the pathogenesis of sciatica.99

Vascular compression of lumbar nerve roots by abnormal epidural venous plexi has been described. The appearance of these plexi was indistinguishable from that of prolapsed intervertebral disc on MRI scan and only became apparent at surgery.44 Pseudoaneurysm of the gluteal artery was also described as a rare cause of lumbar nerve root compression and sciatica.116 Evacuation of the haematoma and decompression of the lumbo-sacral plexus eliminated all sciatic type pain.

Mechanical compression of lumbar nerve roots by an osteophyte around the sacro-iliac joint65 has been described as causing sciatic pain. Also described are sciatic nerve impingement by epidural adhesions,87 uterine fibroids,10 and cyclic sciatica associated with endometriosis in the area of the nerve root.51 82

Piriformis syndrome is a condition that has provoked considerable interest in recent years. The most common anatomical arrangement between the sciatic nerve and the piriformis muscle is that an undivided nerve passes below the muscle, seen in approximately 80% of cases. The whole nerve, or one or both divisions, may also pass through the piriformis muscle. In this situation, contraction of the piriformis muscle may lead to compression and inflammation of the sciatic nerve, with resultant neuralgia. This condition can be treated with injection of steroid to reduce inflammation or botulinum toxin to the muscle to reduce tone.8

Natural history of sciatica

Most patients with acute sciatic neuralgia respond to conservative symptomatic management and resolve over a period of weeks to months.111 However, some do not and require surgery. Approximately 10–40% develop into chronic pain syndrome, which may be called 'failed back surgery syndrome'.5 8 Unfortunately at present, it is difficult to predict at an early stage those who are more likely to have a poor outcome.

A 10 yr observational study of 280 patients, hospitalized with sciatica and confirmed disc herniation, showed that most patients with sciatica could recall an episode of low back pain in their 20s, usually provoked by trauma. Radicular symptoms usually appeared approximately 10 yr later, after an episode of low back pain lasting days to weeks, usually without a definite precipitating factor. This led to a peak onset of sciatica occurring around the age of 40.112

This initial phase of sciatica frequently responds to conservative management. When 214 patients with an acute onset of sciatica corresponding to L5 or S1 were treated with 1 week of bed rest, followed by gradual mobilization and simple analgesia, mean VAS for leg pain had dropped from 54 to 19 within 4 weeks.111 The double-blinded, placebo controlled use of piroxicam in half of the patients did not offer any advantage in recovery, but increased the incidence of adverse effects. Overall, 70% of patients reported a marked reduction in back and leg pain and improved functionality within 4 weeks and 60% had returned to work. After 1 yr, 32% had ongoing problems that still restricted work and leisure activities. A previous history of sciatica was the only risk factor identified with a poor outcome. A total of four patients underwent surgery in the first year.111

A number of studies have been conducted looking at the natural history of symptomatic and asymptomatic herniated lumbar discs. In 11 patients in the non-operative arm of a previous trial with documented disc extrusion by CT scan and corresponding radiculopathy, patients were treated conservatively with simple analgesia and re-scanned 8–77 (median 25) months later. With conservative management, disc herniations had reduced in size by 0–50% in two patients, by 50–75% in four patients, and by 75–100% in five patients, respectively, that is, nine out of 11 (82%) patients had a resolution of 50–100%. MRI scanning revealed that all patients demonstrated a decrease in neural

### Table 2 Non-discogenic causes of sciatica

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<th>Malignancy</th>
<th>Metastatic, bone or soft tissue sarcoma, sciatic neuroma, haemangioblastoma</th>
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<td>Infection</td>
<td>Abscess, caseating disease, discitis</td>
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<td>Vascular compression</td>
<td>Abnormal pelvic venous plexi, gluteal artery</td>
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<td>Bone compression</td>
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<td>Osteophyte</td>
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<td>Gynaecological</td>
<td>Uterine fibroid, pelvic endometriosis (cyclic pain)</td>
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impingement and no patient had evidence of perithecal or perineural fibrosis. Larger extrusions demonstrated the greatest degree of shrinkage and this was more prominent in the cephalo-caudad plane. Significantly, all patients had resolution of symptoms, although this did not necessarily follow the same time course as morphological resolution.91

Similar results were found in a series of 165 patients presenting with an average of 4.4 months acute sciatica.22 Patients were treated conservatively with an average of 3 (range 1–8) caudal epidural steroid injections. Those who failed to respond to epidural steroid were offered surgery. Follow-up scans were performed in 106 patients after 1 yr and compared with the originals. A total of 23 (14%) went on to have surgery within the first year. This study also showed that larger disc herniations were more likely to resolve than focal or generalized disc bulges. Of the 84 documented cases of disc herniation or sequestration, a total of 64 (76%) showed complete or partial resolution after 1 yr. In contrast, of the 22 cases of generalized or focal disc bulge, 18 (82%) were unchanged. Significantly, there were no radiological differences in initial disc appearance between those who responded well to conservative management and those who went on to require surgery. Patients who eventually required surgery had a greater reduction in straight leg raising and had had more epidural steroid injections.22

The tendency for larger disc herniations to resolve more completely than bulging discs was also shown in a group of 77 patients with unilateral leg pain. Repeat MRI scanning demonstrated that large disc herniations with migrating nucleus pulposus were more likely to resolve partially or completely than those herniations where nucleus pulposus was continuous with the main body of the nucleus, that is, disc protrusions. Clinical outcome was closely related to morphological changes on MRI and morphological changes tended to lag behind clinical improvement.63

This appears to show a strong relationship between disc herniation, pain, and subsequent resolution; however, lumbar disc abnormalities are a relatively common finding in asymptomatic individuals. In MRI scans of 67 adults with no history of back or leg pain, about one-third had a substantial abnormality.11 Herniated nucleus pulposus occurred in 21%. 22%, and 36% of those aged 20–39, 40–60, and more than 60 yr, respectively, whereas generalized disc bulging occurred in 56%, 59%, and 79%, respectively. Of those more than 60, 21% had a spinal stenosis, and there was a strong correlation on disc degeneration with age.11 Similar results occurred in MRI scans of 98 asymptomatic volunteers, which showed only 36% of them had normal intervertebral discs. A single disc bulge was seen in 52%, disc protrusion in 27%, and extrusion in 1%. Abnormalities were seen at more than one level in 38%.53

Even higher rates of disc abnormality were observed when asymptomatic volunteers were selected from a cohort who had been matched according to age, sex, and occupational risk with a group of 46 patients undergoing surgery for symptomatic disc herniation. Within this asymptomatic cohort, disc herniation occurred in 76% of volunteers and 21% had neural compromise. The major differences between the asymptomatic and surgical group of patients were disc extrusions (35% vs 13%) and neural compromise were significantly more common in the surgical group (83% vs 21%, P=0.0001).13 A follow-up study was conducted on the same group of asymptomatic volunteers after 5 yr. Questionnaires revealed that 41.3% had suffered one episode of benign back pain. Four volunteers had experienced low back pain within the last 7 days and six individuals (13%) had had to consult a physician regarding back pain. Significantly, despite the high incidence of disc abnormality, none had experienced sciatica pain in the intervening period. In the 41 who consented to a repeat MRI scan, the morphological findings in the majority of patients had not changed with disc herniation in 73% with no change in incidence of neural compromise.14

In summary, disc bulging and protrusions are relatively common in asymptomatic individuals whereas extrusions are rare and sequestrations are not seen. In high risk but asymptomatic volunteers, disc abnormalities were very common, but there was a lower incidence of neural compromise. This again emphasizes the complex interaction between nerve root inflammation and compression that seems to be the cause of sciatica neuralgia. The majority of cases of sciatica are self-limiting and respond to conservative measures. CT and MR scanning of affected individuals appear to show a correlation between resolution of disc abnormalities and symptoms, although morphological improvement lags behind clinical improvement. Larger disc extrusions appear to resolve more completely than generalized disc bulging.

Role of epidural steroid injections in treating sciatica
As with all other forms of neuropathic pain, sciatica is a condition that is best approached from a multi-modal, multi-disciplinary perspective. Pharmacotherapy with tricyclic antidepressants, anti-seizure drugs, and simple and opioid-based analgesics is the cornerstone of management of this condition. Physical therapy is an important compliment to pharmacotherapy and plays a vital role in the management of sciatica. Other non-pharmacological approaches that may be considered include psychotherapy, cogno-behavioural therapy, spinal cord stimulation, epiduroscopy with adhesion lysis and acupuncture (Table 3).

However, the role of epidural steroid injections in the treatment of sciatica has generated much discussion and debate over the last 50 or so years,66 and studies have produced highly variable results. Despite the lack of
consistent results in clinical trials, lumbar epidural steroid injection (LESI) has become firmly established and is widely practiced in the management of sciatica.

Discovered in the mid 1930s, the immunosuppressant and anti-inflammatory properties of corticosteroids are well known.29 If one accepts that sciatic neuralgia arises from a combination of inflammatory, immunological, and mechanical factors leading to nerve root oedema, then these effects of steroids should reduce swelling and nerve root impingement. This is the basis for the practice of LESI for sciatic neuralgia. By injecting into the epidural space, the steroid directly bathes lumbar nerve roots, leading to a rapid effect, with smaller dose requirement.

Despite the theoretical basis, and longevity of practice of LESI for sciatica, there is still uncertainty about the efficacy of the procedure. Although numerous clinical studies have been conducted over the years, they have produced inconsistent results. Many of these studies have been flawed methodologically, and in a review of 12 studies, only four were judged to be methodologically sound.62 However, meta-analyses of pooled data from epidural steroid studies have produced favourable results. A meta-analysis of 11 trials110 with a total of 907 patients on the use of LESI for sciatica, using the end-point of near or total pain relief as a beneficial outcome, revealed the OR for short-term benefit (up to 60 days) with LESI for sciatica was 2.61 (95% CI 1.9–3.77), compared with placebo. OR for long-term benefit was reduced at 1.87 (95% CI 1.31–2.68). This beneficial effect was independent of the route of injection, with OR for benefit being 3.8 (95% CI 1.36–10.6) for the caudal route and 2.43 (1.77–3.74) for the lumbar translaminar route.110 Using numbers needed to treat (NNT)71 in studies looking at short-term benefit (1–60 days), the NNT for >75% pain relief was 7.3, meaning that for every 7.3 patients treated, one would get more than 75% pain relief for up to 60 days. However, for short-term relief of pain by 50%, the NNT was 3. In studies looking at long-term benefit, that is, 12 weeks to 1 yr, the NNT for 50% pain relief was 13.71

These meta-analyses suggest that any beneficial effect of LESI for sciatica is relatively short-lived. This was reflected in the results of two recently conducted studies. One study, in 158 patients, showed that the benefit of epidural steroid, evident after 3 and 6 weeks had disappeared by 3 months and, after 12 months, there were no differences in incidence of back surgery between groups.24

Another study in 36 patients showed that the addition of three LESIs to a standardized regime of bed rest and non-steroidal anti-inflammatory drug (NSAID) analgesia with tramadol for severe pain, led to improved straight leg raising (SLR) only at 2 weeks. There were no significant differences in any outcome measures at 6 weeks or 6 months.20

The problem with epidural injections, either by the caudal or by the translaminar route, is that there is no guarantee that the steroid reaches the target nerve root. This depends on spread of injectate, to not only the appropriate level, but also the ventral part of the epidural space where the nerve roots are located. This problem can be overcome by transforaminal nerve root injections, where the steroid is injected directly around the nerve root in question with the aid of fluoroscopy.

Perhaps not surprisingly, there is a lack of consistency in outcomes in the studies that have been conducted in this area. In a double-blind study, 160 patients with unilateral sciatica were randomized to receive a transforaminal nerve root injection of either methyl-prednisolone 40 mg ml\(^{-1}\) and bupivacaine 0.5% or saline. This study showed that at 2 weeks there was a significant improvement in all outcome measures except lumbar flexion in the steroid group. However, at 4 weeks, there were no significant differences in any outcome measures. After 3 and 6 months, pain levels were actually lower in the saline group, raising the possibility of a rebound effect. After 1 yr, there was no difference in incidence of patients who went on to require surgery.56 In contrast to this, an unblinded, randomized study of 48 patients with leg pain and documented herniated nucleus pulposis compared transforaminal LESI, using betamethasone 9 mg and lidocaine 2% (1.5 ml), with saline trigger point injections. Patients were followed for an average of 16 months. At the end of follow-up, there was a significant difference in favour of the transforaminal group in terms of disability score, VAS, lumbar flexion, and patient satisfaction.107 This study demonstrated a potential long-term benefit of transforaminal LESI, although the lack of blinding was a significant limitation of the study.

Despite the longevity of the practice of LESI for sciatica, there remain a number of unresolved issues. Questions regarding the ideal number of injections, the ideal volume, and content of injectate (local anaesthetic or steroid), the ideal level for injection, the need for fluoroscopy, most effective route (i.e. transforaminal vs translaminar), and safe maximum number of injections and dosage of steroid that can be administered over a given period remain unanswered.

<table>
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<th>Summary of methods of management of sciatica</th>
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<td>Tricyclic antidepressants, that is, amitriptyline and related compounds</td>
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<td>SNRIs, that is, duloxetine, venlafaxine</td>
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<tr>
<td>Opioid analgesics, that is, oxycodone, tramadol, MST</td>
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Complications of epidural steroid injections

LESI, like any other invasive procedure, is associated with an element of risk. A comprehensive review of the complications, looked at 65 studies involving epidural or subarachnoid steroid injections in 7315 patients. This showed that overall, epidural steroid injection is a fairly safe procedure where complications are uncommon and usually temporary. However, serious complications do occur but fortunately are rare.\(^1\) Hazards of LESI may be classified as side-effects of injected drugs, technical hazards of the injection technique, and minor and major neurological sequelae.

The rationale for epidural placement of steroid is that the drug is deposited directly on sciatic nerve roots, thereby minimizing the required dose and systemic absorption and associated metabolic adverse effects. However, it has been clearly demonstrated that epidural injections of even relatively small doses of steroid can have metabolic effects on the pituitary adrenal axis. A single epidural injection of methyl-prednisolone 80 mg resulted in marked suppression of cortisol secretion and impaired ability of the adrenal cortex to respond to adrenocorticotropic hormone (ACTH). Maximal after 1 week, this suppression persisted for up to 3 weeks. Plasma levels of methyl-prednisolone were undetectable throughout the 3-week period, suggesting that the steroid effect was due to subarachnoid rather than systemic absorption of the drug.\(^52\)

Similar results were noted after epidural injections of triamcinolone 80 mg. Suppression of ACTH and cortisol secretion, which occurred within 45 min of injection persisted for more than 30 days. Adrenal suppression was even more profound when injections were preceded with midazolam sedation. Furthermore, patients showed a reduced secretion of cortisol in response to synthetic ACTH 34 days after the last epidural steroid injection.\(^58\) These two studies demonstrated that even isolated epidural injections of therapeutic doses of steroid may result in marked and prolonged suppression of pituitary and adrenal function.

Overt cushingoid side-effects have been noted after LESI for sciatica. Although one report came after the use of very high doses of steroid, that is, 300–600 mg methyl-prednisolone over a 3-day period,\(^32\) another case report followed a single epidural dose of methyl-prednisolone 80 mg. Furthermore, this condition persisted for 12 months.\(^106\) Other systemic effects of steroid use, such as weight gain, hypertension, congestive heart failure,\(^1\) and menstrual irregularity,\(^23\) have all been reported after epidural steroid injection. Clearly, there is some systemic uptake of steroid after epidural injection which may be responsible for the therapeutic effects of the procedure.

The most common technical complication associated with LESI is dural puncture. An analysis of 11 studies involving 907 patients revealed an incidence for dural puncture of 2.5% with headache occurring in 2.3% of cases after LESI. In addition, pain was increased in 1.9% of patients.\(^110\) It is important to recognize dural puncture in order to prevent inadvertent subarachnoid injection of potentially neurotoxic drugs and additives.

Intravascular injection is another possibility with LESI. One large multi-centre study of 1219 contrast-enhanced, fluoroscopically guided LESI procedures showed that intravascular needle placement occurs with 10.9% of caudal, 10.8% of transforaminal, and 1.9% of translaminar injections, and was twice as likely to occur in patients more than 50 yr.\(^100\)

Minor neurological effects associated with LESI include transient increase in sciatica pain, vasovagal reaction in response to the deep somatic pain of the injection, headache, dizziness, stiff neck, flushing, urinary retention, hypotension, and vomiting. These effects tend to be transient and usually require no treatment.\(^4\)

Serious complications such as nerve root damage, epidural haematoma, and epidural abscess also occur but fortunately are rare. Indeed, these complications are considered so rare, they often merit individual case report publications.\(^25\ 40\ 114\) Epidural abscess is always a potential threat, particularly when injecting steroid. Again, traditionally considered to be an ‘almost theoretical’ hazard of epidural anaesthesia, recent evidence suggests that the incidence of this potentially devastating complication may have been underestimated.\(^42\) The majority of epidural abscesses are spontaneous. In one case series of 915 patients, only 3.9% of abscesses were associated with epidural anaesthesia.\(^86\) A number of studies have tried to estimate incidence of epidural abscess after anaesthetic intervention but there is much variation in quoted figures. For example, 1:800 in surgical patients, although within the same series, no abscesses were reported in 5000 obstetric patients.\(^83\) Other estimates of incidence range from 1:1930 for all epidural interventions,\(^109\) 1:2000 for obstetric epidurals,\(^61\) up to 1:505 000 in consecutive obstetric epidurals.\(^95\)

There are no specific figures for incidence of epidural abscess after LESI. The immunosuppressant qualities of steroid led one author to consider LESI as a specific risk factor for epidural abscess.\(^19\) This is balanced against the lack of epidural catheterization which may be related to the overall risk of abscess formation.\(^32\) At the time of writing, a national audit is being conducted in the UK collecting all episodes of major complication after neuraxial anaesthesia. Subgroup analysis of data from this audit may provide an accurate estimate of the number of LESIs conducted over a year in the UK along with the number of associated complications.

In terms of efficacy, large meta-analyses\(^71\ 110\) have demonstrated unequivocally that LESI is an effective treatment for sciatica. Although this benefit may be of short duration and offers no long-term advantage, given that most cases of acute sciatica are naturally of limited
duration, performing this procedure to accelerate the natural resolution of pain seems reasonable.

When consideration is given to performing LESI on a patient with sciatic neuralgia, it is vital that both the patient and the physician have a clear understanding of the balance between risk and benefit. Patients should be informed that any benefit of this procedure is likely to be of relatively short duration and that it may be necessary to undergo repeat injections. Patients should also be made aware that there is relatively high chance that they will get no benefit at all. Patients should also be made fully aware of the potential risk they incur before giving consent. Information about potential systemic effects of the steroid injectate should be given. This is particularly important for diabetic patients and women of reproductive age who may experience menstrual irregularity. Patients should also be made aware of the common minor side-effects listed earlier, particularly a transient increase in pain. Finally, in the authors’ opinion, although rare, patients should also be made fully aware of potentially serious hazards such as temporary or permanent neurological damage, epidural haematoma, and abscess. It could be argued that these events are so rare, informing patients of them will only discourage them from having the procedure. However, given that a major neurological complication, no matter how rare, can have such enormous impact on quality of life, patients must be informed of this before they give genuine informed consent. Unfortunately, we are as yet still unable to accurately quantify the potential risk for such a major complication. Hopefully, this information will soon become available in order to allow patients to come to an informed decision about whether the risk justifies the benefit of this procedure.

In the authors’ opinion, the most important question about efficacy of LESI is not if it works but how it works. Is it due to a direct action of steroid on sciatic nerve roots or simply due to systemic uptake and circulation from the vascular epidural space? It has even been suggested that methyl-prednisolone may act by a local anaesthetic action on sciatic nerve roots, rather than by an anti-inflammatory effect.12

Systemic effects of corticosteroids after LESI have been described, indicating that there is a vascular uptake of the drug.32 52 58 106 Could this systemic uptake be the source of the therapeutic effect of the drug? High doses of i.m. dexamethasone were shown to have beneficial effects in patients with pain associated with herniated lumbar intervertebral discs.41 Furthermore, two animal studies have shown that the epidural placement of methyl-prednisolone and triamcinolone causes no or minimal inflammatory changes, respectively, in epidural nerve roots.28 30 This suggests that both particulate and soluble preparation of steroid may not cross the dura surrounding lumbar nerve roots.

Steroids act at a cellular level by influencing the transcription of particular genes leading to increased synthesis of anti-inflammatory and decreased synthesis of pro-inflammatory proteins.54 This is a delayed effect that takes hours to occur, making one question whether direct placement of drug into the epidural space is really of any benefit.

In skilled hands, epidural steroid injection is fairly safe, and complications are unusual. However, the concept that it may help but probably will not do any harm is not a valid justification for performing this or any other procedure. Epidural injection is a skilled procedure which limits the amount of practitioners who can perform it, leading to increased delay, and possibly expense for patients. Although rare, hazards are real and may be serious.1 This concept applies more so for translaminar injection of steroid, which has the added (thus far unquantified) hazard of exposure to ionizing radiation.

This goes back to the important question in relation to use of epidural steroids for sciatica regarding the mechanism of action. Further studies comparing epidural with systemic steroid are urgently required. If the effect is demonstrated to occur locally at the affected nerve root, epidural steroid injection is fully warranted. However, if a systemic effect could be demonstrated, translaminar and transforaminal injections would be unnecessary, making it much easier and cheaper for patients to get effective treatment.

Conclusion
Sciatica is a common condition that is a major cause of work absenteeism and a major financial burden to both industry and health service provision. Although the intervertebral disc has been firmly implicated in the pathophysiology of this condition, the exact nature of the relationship to disc, nerve, and pain is not yet certain. Current evidence suggests that the nucleus pulposus provokes a strong inflammatory response in sciatic nerve roots and this is a likely source of pain. Evidence also exists which suggests that inflammation, abnormal immune factors, and mechanical deformation of the nerve is required to produce pain, and this seems a likely combination. However, herniation of the nucleus pulposus is not the only cause of sciatica and other causes should not be forgotten. Fortunately, most cases of sciatica are self-limiting and pain tends to resolve within a matter of months. However, some cases progress to become chronic, and unfortunately, these can be difficult to treat.

Epidural steroid injection remains a popular treatment for the acute phase of sciatica. Large meta-analyses have demonstrated that this is an effective treatment for at least the acute phase of sciatica. However, the question of the whether this is a direct effect or due to systemic uptake and delivery of drug from the vascular epidural space needs to be resolved.
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