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EVIDENCE-BASED REVIEW

Update of evidence-based interventional pain medicine according to clinical diagnoses

6. Persistent spinal pain syndrome type 2

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Abstract

Introduction: Persistent Spinal Pain Syndrome (PSPS) refers to chronic axial pain and/or extremity pain. Two subtypes have been defined: PSPS-type 1 is chronic pain without previous spinal surgery and PSPS-type 2 is chronic pain, persisting after spine surgery, and is formerly known as Failed Back Surgery Syndrome (FBSS) or post-laminectomy syndrome. The etiology of PSPS-type 2 can be gleaned using elements from the patient history, physical examination, and additional medical imaging. Origins of persistent pain following spinal surgery may be categorized into an inappropriate procedure (eg a lumbar fusion at an incorrect level or for sacroiliac joint [SIJ] pain); technical failure (eg operation at non-affected levels, retained disk fragment, pseudoarthrosis), biomechanical sequelae of surgery (eg adjacent segment disease or SIJ pain after a fusion to the sacrum, muscle wasting, spinal instability); and complications (eg battered root syndrome, excessive epidural fibrosis, and arachnoiditis), or undetermined.

Methods: The literature on the diagnosis and treatment of PSPS-type 2 was retrieved and summarized.

Results: There is low-quality evidence for the efficacy of conservative treatments including exercise, rehabilitation, manipulation, and behavioral therapy, and very limited evidence for the pharmacological treatment of PSPS-type 2. Interventional treatments such as pulsed radiofrequency (PRF) of the dorsal root ganglia, epidural adhesiolysis, and spinal endoscopy (epiduroscopy) might be beneficial in patients with PSPS-type 2. Spinal cord stimulation (SCS) has been shown to be an effective treatment for chronic, intractable neuropathic limb pain, and possibly well-selected candidates with axial pain.

Conclusions: The diagnosis of PSPS-type 2 is based on patient history, clinical examination, and medical imaging. Low-quality evidence exists for conservative interventions. Pulsed radiofrequency, adhesiolysis and SCS have a higher level of evidence with a high safety margin and should be considered as interventional treatment options when conservative treatment fails.

KEYWORDS
back pain, evidence-based medic

INTRODUCTION

This article is part of the series: "Update of Evidence-based interventional pain medicine, according to clinical diagnoses." In the previous series, the topic failed back surgery syndrome was discussed in the chapter: Lumbosacral radicular pain.[1]

The term Failed Back Surgery Syndrome (FBSS) is misleading as it implies causation—and does not address other causes and factors involved in developing chronic pain after spinal surgery. Proposals have been made to replace the term FBSS with the more appropriate persistent spinal pain syndrome (PSPS)-type 2.[2] It is estimated that 10%–40% of patients may experience persistent or recurrent pain after spinal surgery, being higher for larger surgeries aimed at treating more advanced pathology and repeat operations.[3,4]

Failed Back Surgery Syndrome was defined as a condition where a patient experiences recurrent pain and discomfort in the back and/or legs after undergoing one or more spinal surgeries.[5]

Two primary types of PSPS can be distinguished in general: type 1 with chronic axial and/or limb pain occurring without any spinal surgery, and type 2 with chronic axial and/or limb pain occurring after spinal surgery. These groups can be further subdivided according to the type of pain, neuropathic, nociceptive, and nociplastic or a mixed form of pain.[2]

In this chapter we will focus on patients with PSPS-type 2, defined as pain that occurs or persists after spine surgery, which can be divided into the following categories with the potential with overlap[2]:

- Directly caused by the surgical intervention (eg surgical complication);
- indirectly caused by the surgical intervention (eg biomechanical changes);
- recurrent pain after an initially successful surgery (eg recurrent pathology);
- other symptoms not relieved by or related to surgery.[2] (eg myofascial pain, central sensitization)

Symptoms of PSPS-type 2 can be complex, with different possible presentations including but not limited to back pain, limb pain, paresthesia, numbness, weakness, and limited mobility. These symptoms often significantly impact a patient's quality of life by hindering activities of daily living (ADL) and may require conservative or interventional pain management and/or rehabilitation to address.

Treatment options for PSPS-type 2 include physical therapy, pharmacological treatment, minimally invasive interventional procedures (eg epidural steroid injections, pulsed radiofrequency, or adhesiolysis), neuromodulation, and novel surgical interventions. Nevertheless, the management of PSPS-type 2 has proven to be challenging. For example, PSPS-type 2 is often refractory to pharmacological therapy.[6–8] Revision spine surgery, with the aim of removing epidural fibrosis, is reported to be effective only in 5%–30% of patients.[2,6] When the decision to perform revision surgery is made, different procedures can be considered. In most patients, decompression including laminectomy with disk resection targeted at the level(s) postulated to be the origin of the spinal or radicular pain will be performed. However, in case of instability or spondylolisthesis, fusion procedures are frequently offered.[9]

A systematic review identified six studies reporting the possible etiologies of PSPS.[10] Twenty-two different etiologies were identified including pathoanatomical, neurophysiological, physical/mechanical, peripheral pain generators, surgical and "other" etiologies. These findings clearly illustrate the complexity of the pathogenesis of PSPS and the challenges for the management of this syndrome.[10]

Multiple pain sources can be identified in patients with PSPS, including neuropathic pain due to foraminal stenosis or recurrent disk herniation; mechanical pain, such as facetogenic or sacroiliac joint pain; nociplastic pain, nonspecific back pain, as individuals with central sensitization are more likely to fail spine surgery; and mixed phenotypes.[11] A broad differential diagnosis should always be made in patients with PSPS-type 2. It remains important to rule out "red flags" like fractures, neoplasm and infection.[12] A thorough history and physical examination should always be performed as PSPS is essentially a clinical diagnosis.

METHODOLOGY

This narrative review is based on the article "lumbosacral radicular pain" published in 2010.[1] In 2015, an independent company, Kleijnen Systematic Reviews (KSR), performed a systematic review of the literature for the period 2009–2015 based on existing systematic reviews (SRs) and randomized controlled trials (RCTs).[13,14] For this article, an updated search was conducted for the period 2015–2023, using "failed back surgery syndrome" or "persistent spinal pain syndrome" and "pain" associated with various interventional pain management techniques such as "epidural" and "steroid" or "corticosteroid"; "radiofrequency" or "pulsed radiofrequency"; "adhesiolysis"; "epiduroscopy" and "spinal cord stimulation". Additionally, authors searched the reference lists of selected articles and could select other relevant articles. We mainly searched PubMed, using text words. Systematic reviews and meta-analyses were retrieved as well as randomized controlled trials and large cohort studies, with the latter mostly limited to the surveillance of side effects and complications.

ANATOMY

Anatomy of the epidural space

Epidural space literally means the space surrounding the dura mater. It is also referred to by some authors as "extradural space" or "peridural space," while others use these terms for the space surrounding the dural cuffs and nerve roots (ie the space surrounding the dorsal root ganglion, DRG, see Figure 1).[15,16]

The epidural space is bordered *anteriorly* by the posterior longitudinal ligament (PLL), the vertebral bodies and the intervertebral disks; *laterally* by the intervertebral foramina and the pedicles of the vertebral arches; *posteriorly* by the vertebral arches and the ligamenta flavum; and *sacrally* by the fused sacral vertebral arches. Since the dural sac ends at the level of the S2 vertebral body, only epidural fatty tissue, the filum terminale externum and the proximal parts of the nerve roots S2-Cocc1 are found in the most caudal part of the epidural space.

The caudal boundary of the sacral epidural space is formed by the sacrococcygeal membrane. This membrane seals the sacral hiatus but is absent in about 10% of patients. This is the structure that is used for caudal access to the lumbosacral epidural space for epiduroscopy and caudal blocks.

Tissue composition

The epidural tissue consists of loose areolar connective tissue and varying amounts of fatty tissue, which is currently regarded as "sliding tissue" rather than regular fatty tissue. The contents of the epidural space are variable and depend on the patient's medical and surgical history. In some patients, postoperative connective tissue fills up the entire epidural space at a certain level and it becomes impossible for caudally injected substances to reach the space cranial to this tissue. Surgeons have even confirmed the presence of calcified connective tissue plates during repeat operations of the spine after primary herniated disk surgery, a finding sometimes encountered with epiduroscopy.[15]

The fatty tissue is mainly located in the anterolateral and dorsomedian parts of the epidural space. Laterally, the lumbosacral epidural space communicates with fatty tissue adjoining the spinal column via the intervertebral foramina, although some studies have reported that the epidural space is laterally bounded by the so-called anterior dural or Hofmann ligaments.[15] Finally, intraforaminal ligaments have often been described in the intervertebral foramina, which are thought to serve mostly as fibrous conduits for the emerging nerves.[15]

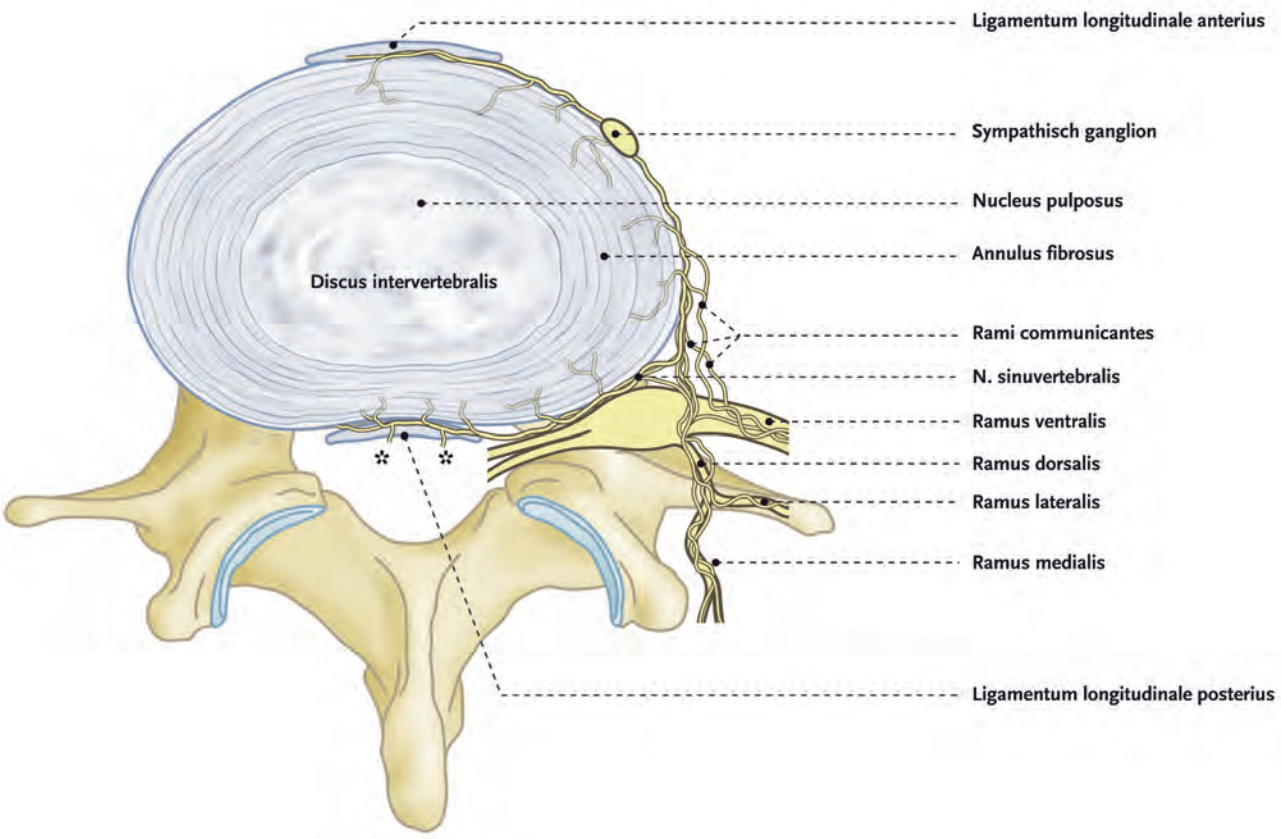

FIGURE 1 Schematic drawing of the lumbosacral innervation. Connections to the dural nerve plexus. Illustration Rogier Trompert Medical Art. http://www.medical-art.eu.

Blood vessels

The epidural space contains arteries and veins supplying the spinal cord. The epidural arteries branch off from segmental arteries. The veins interconnect, thus forming a venous network. This so-called Batson plexus comprises a ventral and a dorsal venous network, which are interconnected (the internal vertebral venous plexus) and drain blood from the vertebral column, especially the vertebral bodies. The ventral plexus is situated between the PLL and the vertebral corpora, while the dorsal plexus lies free in the dorsal epidural space. In the lumbosacral part of the vertebral column, the ventral venous plexus is generally larger compared to the dorsal part, whereas the size of the dorsal plexus increases from the high lumbar to the low thoracic vertebrae.

The venous structures of the plexus are assumed to be valveless. The plexus communicates caudally with the pelvic vein; cranially with venous sinuses in the cranium; and laterally with segmental veins (lumbar veins and intercostal veins) via the intervertebral foramina.

Nerves

All nerves supplying the epidural space branch from the sinuvertebral nerves (Luschka), originating from the rami communicantes of the spinal nerves that return to the epidural space via the intervertebral foramina, ventral to the nerve roots. They form extensive networks, providing sensory innervation for internal parts of the spinal column: the PLL, the vertebral bodies and the posterolateral part of the intervertebral disks, as well as the ventral dura. The dorsal dura is sparsely innervated. Given the intrinsic relationship between the epidural nerves and the sympathetic trunk (through the rami communicantes), all these structures are sympathetically innervated as well.[15]

Dura mater

The dura mater is a strong connective tissue membrane surrounding the cerebral spinal fluid (CSF) space lined with the arachnoidea, sprouting side-branches which contain the anterior and posterior nerve roots, as well as the dorsal root ganglia (DRGs). These side-branches constitute the so-called dural (nerve root) sleeves.

On a transverse section, the dural sleeves are localized in the anterolateral quadrant of the spinal canal, pictorially depicted at the 10 o'clock and 2 o'clock positions on the face of a clock. The anterior part is called the "shoulder," while the posterior part is called the "axilla," corresponding to the shoulder and armpit parts of the sleeves of a jacket. The dural sleeve continues onto the outer layer of the spinal nerve where it becomes the epineurium. Within the intervertebral foramen, the dural sleeve is dorsally bounded by the ligamentum flavum, which is closely associated with the ventral capsules of the facet joints (Figure 2A,B).

Epid: Epidural space

Pathophysiology of radicular pain

Radicular pain is not solely the result of nerve root compression.[17–23] Compression can cause spinal nerve dysfunction with ensuing sensory and/or motor deficits,[24] whereas pain is postulated to require a local inflammatory reaction. This was demonstrated in a study by Howe et al.,[25] whereby compression of a normal peripheral nerve induced short duration pulses but compression of an inflamed peripheral nerve resulted in prolonged firing.[26,27] More recent animal studies have shown that pre-exposure to inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin 1-beta (IL-1b) and cytokine-induced neutrophil chemoattractant 1 (CINC-1) result in thermal and mechanical hyperalgesia in a rodent disk herniation model, but pretreatment with anti-cytokine antibodies resulted in decreased hyperalgesia at different time points, suggesting that the combination of inflammation and compression may be necessary to induce radicular pain. Nonetheless, pressure on the nerve root can by itself cause inflammation with infiltration of macrophages and inflammatory cytokines.[28,29] Compression and/or fixation of the nerve root in the neuroforamen can lead to stretching, resulting in decreased intraneural microcirculation and ischemia, which is postulated to be a common mechanism in central and foraminal stenosis.[30,31] Damage to endoneural blood vessels will lead to breakdown of the blood–nerve barrier causing intraneural edema which further compromises the microcirculation of the nerve root. The long-standing intraneural edema leads to a vicious circle with infiltration of fibroblasts and scar tissue formation which further compromises the nerve root blood supply. Compression of nerve roots leads to changes in axonal flow and altered metabolism of neurotransmitters, thereby further impairing nerve function.[28,32,33] Local demyelination sites start to function as ectopic foci, with ectopic discharges interpreted centrally as altered sensations and/or spontaneous pain.[34]

The nucleus pulposus of the intervertebral disk itself contains a range of proinflammatory interleukines,[18,23,30,35–37] and a tear in the annulus fibrosis can cause large quantities of phospholipase A2 to be released into the epidural space, causing an inflammatory reaction further intensified by the release of TNF-α from mononuclear inflammatory cells.[17–23,27,38]

Spinal fibrosis as a cause of nerve compression may be induced by spinal surgery itself. On the one hand, surgical

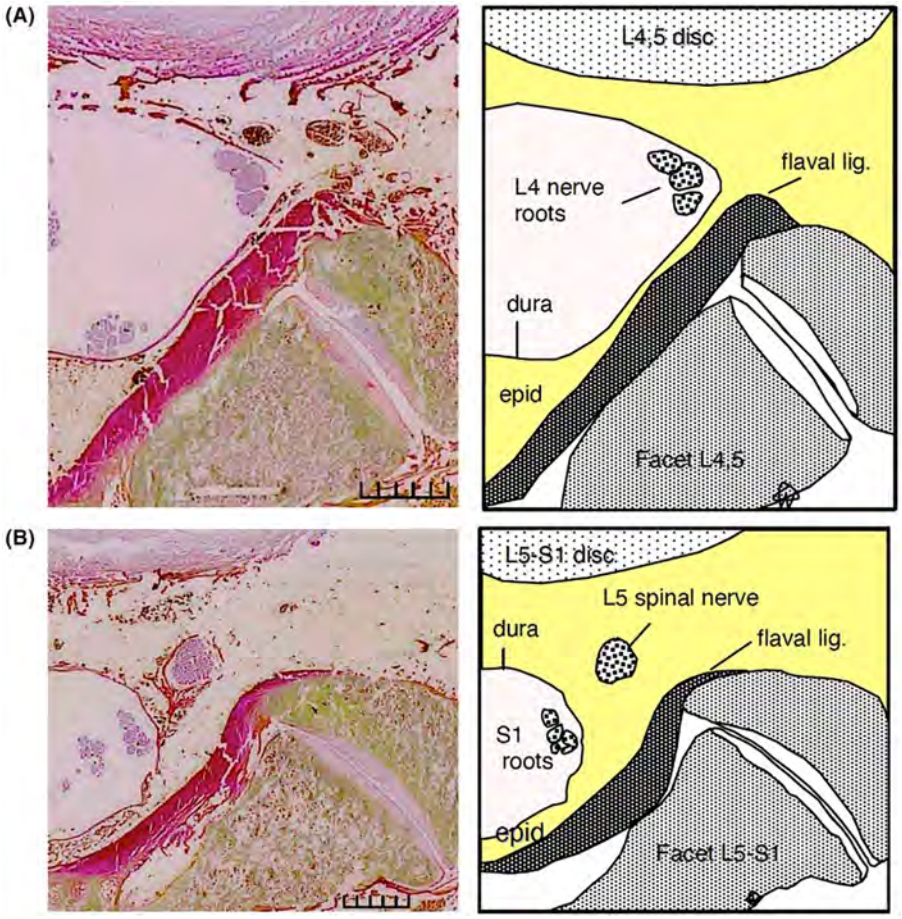

FIGURE 2 Histologic transverse cut of the lower lumbar spinal column with dura and epidural fat tissue at the level of the (A) L4-5 intervertebral foramen L4-5 and (B) L5-S1 foramen. Mallory–Cason trichrome coloring. The proximal part of the dural manchet is closely related to the ligamentum flavum and the facet joint.

repair can restore the nutritional status of the nerve (in terms of nerve growth factor [NGF] supply) as it relieves the nerve root compression; while on the other hand, it induces new tissue trauma, hemorrhage, and contamination with foreign materials which may lead to renewed fibrosis formation. Epiduroscopy performed in patients with chronic radicular pain has demonstrated the presence of epidural fibrosis in nearly 100% of patients, though most studies have failed to demonstrate a positive correlation between epidural fibrosis and clinical symptoms.[39–43] Even in studies where a correlation is established, proving a causative relationship is challenging since the magnitude of pathology and extent surgery are by themselves potential etiologies of both fibrosis and pain.[44]

DIAGNOSIS

The diagnostic workup of a patient with PSPS-type 2 requires the exclusion of serious underlying causes of pain such as infection or malignancy, with the goal of identifying the most probable etiology of the spinal lesion.

History

A careful history taking is mandatory. Symptoms can be very complex since neuropathic, nociceptive and nociplastic symptoms often coexist, with patients who have a strong component of central sensitization more likely to "fail" spine surgery.[11] There are no pathognomonic characteristics that can confirm the diagnosis of PSPS-type 2. History taking should include the duration, onset of pain, localization, presence of neurological symptoms, concomitant psychopathology, localization, as well as characteristics of nociceptive, neuropathic, and neuroplastic pain.

Persisting symptoms, unchanged from the presentation before surgery, are suggestive of inappropriate patient selection, inappropriate surgical procedure, or technical failure (eg retained disk fragment, pseudoarthrosis). Examples include a patient with nociplastic pain or poorly treated psychosocial issues receiving surgery without management of these factors, as well as wrong-level or type surgery (eg fusion for radicular symptoms). However, even the identification of technical surgical failures can be fraught with challenges, with studies finding little difference in clinical outcomes after

decompression in patients with a postsurgical lumbar disk herniation and those without an MRI-confirmed herniation and numerous studies finding a poor correlation between lumbar fusion success (ie pseudoarthrosis) and clinical outcomes to include pain relief, function, and satisfaction.[45,46]

Different pain after surgery, with initial improvement of the symptoms followed by a different presentation, can be indicative of epidural scar tissue, loss of lordosis or paraspinal muscle atrophy, arachnoiditis, adjacent segment disease leading to facetogenic or discogenic pain, or the development of spinal instability following multilevel decompression. In this scenario, timing of symptom development may provide important clues on etiology. For example, arachnoiditis, battered root syndrome, and epidural fibrosis will manifest weeks to months after surgery; on the other hand, biomechanical sequelae of surgery may take years to develop. Sacroiliac joint pain can fall into this category or "inappropriate section" as many patients with an SIJ pain generator undergo inappropriate lumbar spine surgery, while fusion to the sacrum can also cause and accelerate both extra- and intra-articular pathology.[47–50] In post lumbar fusion patients, the rate of positive diagnostic SIJ blocks is estimated to range between 30% and 50%.[51–53] Among individuals whose pain improved but subsequently returned in a similar pattern, one must consider recurrence of the baseline pathology (eg re-herniation, dislodgement of hardware).

Recurrent pain after surgery, such as radicular pain in a similar distribution, can indicate re-herniation, which has an incidence of 10% to over 25% at 2 years.[54] Since patients with herniated disks usually have full-thickness tears, the threshold for re-herniation is much lower than in functionally intact disks.

Red flags should be excluded by evaluating for signs of infection, malignancy, or recent trauma.[55] As alluded to above, psychological screening is necessary to identify possible factors contributing to the maintenance of chronic pain such as depression, anxiety, poor coping skills, and catastrophizing.

Physical examination

Findings of the physical examination in patients with PSPS-type 2 are often nonspecific. The Lasègue test, also known as the straight leg raising test, can be performed to identify the presence of lower lumbar radicular pain.[56] Although this test has high sensitivity, the specificity is low; this is in contrary to the crossed Lasègue test, which has low sensitivity but high specificity.[57] For mid- and upper level radiculopathy, the femoral stretch test has high sensitivity and specificity.[58] Attention should be paid to any neurological signs of paresis, sensory changes, or loss of reflexes.[59] Signs of central sensitization like temporal summation, impaired conditioned pain modulation, multiple hypersensitivity reactions, or sensitivity other stimuli such as lights, sounds, and smells should be evaluated.[60,61]

Additional testing

Plain radiography including flexion-extension films and whole-spine anteroposterior and lateral views allow evaluation of the surgical site, spinal alignment, the presence or absence of spinal imbalance, and interval degenerative changes.[15]

Magnetic resonance imaging (MRI) with gadolinium enhancement can facilitate the identification of spinal canal or neuroforaminal stenosis and recurrent disk herniation and distinguish it from scar tissue.[62] Computed tomography (CT) can be useful for assessing the integrity, position, osseous fusion, and complications of the spinal instrumentation. CT is indicated in the first weeks after spinal surgery to evaluate the presence of foraminal stenosis or vertebral fusion, as MRI scanning may be difficult to interpret in this period.[55] In patients with hardware incompatible with MRI, CT-myelography can provide detailed delineation of pathological conditions involving the thecal sac and its contents and may be particularly beneficial in patients of suspected arachnoiditis and arachnoid cysts.[63]

Differential diagnosis

Differential diagnosis should aim to rule out or confirm serious underlying disease as identified with the aid of "red and yellow flags." Recent trauma or a long history of corticosteroids use can predispose patients to vertebral compression fracture. Metastasis should be excluded in patients with a history of malignancy or constitutional symptoms such as unexplained weight loss.[55] Fever and other symptoms of infection as well as a history of immunosuppression can lead to the diagnosis of epidural abscess or spondylodiscitis, which may take weeks or months to manifest. Table 1 gives an overview of the differential diagnoses of PSPS-type 2.

TREATMENT OPTIONS

PSPS-type 2 not attributed to spinal instability or neural compromise can present with a variety of symptoms including back pain, radicular pain, and radiculopathy.[10,12] Conventional treatments and minimally invasive procedures for radicular pain are discussed in the article: "1. Lumbosacral radicular pain."[64]

Conventional medical management

It is generally accepted that physical rehabilitation may help maintain or improve a patient's level of functioning

TABLE 1 Differential diagnosis of PSPS-type 2.

Mechanical	Spinal instability
	Pseudo-arthrosis/nonunion after spinal fusion surgery
	Adjacent level disease
	Spondylolisthesis
	Muscle wasting
Fracture	Traumatic spinal fractures
	Vertebral insufficiency fractures
Infectious	Arachnoiditis (rarely infectious)
	Epidural abscess
	Spondylodiscitis
Radicular	Cauda equina syndrome
	Epidural fibrosis
	New-onset radicular syndrome (eg due to new disk herniation)
Various	Involvement of other axial pain generators (eg facet joints, sacro-iliac joint, vertebrogenic or discogenic pain)
	New onset spinal malignancy or metastasis
	Autoimmune disorders (eg Guillain–Barré, multiple sclerosis)
	Other new or recurring chronic pain conditions
	Inflammatory disorders (eg spondyloarthropathies, rheumatoid arthritis)

but a systematic review focused on the treatment of PSPS-type 2 found low-quality evidence for the effectiveness of exercise, rehabilitation, manipulation, and behavioral therapy.[7] A systematic review on rehabilitation following primary lumbar disk surgery found strong evidence that intensive exercise programs are more effective for functional status and faster return to work compared to mild exercise programs in the short term (3–6 months); however, at long-term (12 months) follow-up, no significant differences were observed between programs.[65]

A systematic review by Amirdelfan et al showed scant evidence for pharmacological treatment in patients with PSPS type 2.[7] Reviews on back pain may provide more generalizable evidence than those on neuropathic and non-neuropathic pain. One review by Bhatia et al. found no evidence supporting acetaminophen/paracetamol, gabapentinoids, tricyclic antidepressants, and serotonin-specific reuptake inhibitors for radicular pain, but moderate evidence supporting duloxetine for mechanical back pain with one small randomized crossover trial demonstrating efficacy for lumbosacral radiculopathy.[66,67] For nonsteroidal anti-inflammatory drugs, there was evidence for a small, clinically questionable effect, and low-quality evidence supporting short-term benefit for muscle relaxants in acute pain. Botulinum toxin had some evidence supporting efficacy in individuals with high muscle tone based on mostly industry-sponsored studies. Opioids were found to provide modest benefit for acute and intermediate term pain but were associated with significant harms.

Beside pharmacological therapy, rehabilitation and physical therapy, psychological factors can play an important role in chronic pain and PSPS type 2. Multidisciplinary pain management can also treat the negative pain experience and psychological consequences of chronic pain.[68,69] Multidisciplinary pain programs are based on the biopsychosocial model of Loeser.[70] Multidisciplinary treatments can consist of a combination of rehabilitation, physical therapy, pain treatments, and psychological approaches like cognitive behavioral therapy, biofeedback, acceptance and commitment therapy and the improvement of coping mechanisms in individuals with chronic pain.

Interventional management

Epidural steroid injection

Although epidural steroid administration is recommended in patients with PSPS-type 1 with subacute lumbosacral radicular pain, large RCT's in PSPS-type 2 are lacking.[71–75] Routine use of epidural steroid injections in patients with PSPS-type 2 for longer than 6 months is therefore not recommended.

Pulsed radiofrequency treatment

In patients with chronic lumbosacral radicular pain, pulsed radiofrequency of the dorsal root ganglia can be considered. This treatment has not been studied specifically in patients with PSPS-type 2,[71] but in a cohort study containing 23% of patients with PSPS type-2, the outcome was similar compared to PSPS type-1.[76] A good clinical outcome, defined as a reduction in pain intensity of at least 2 points or a global perceived effect reporting "full recovery" or "much improvement" at 6 months, was reported by 55.4% of patients.

Epidural adhesiolysis and spinal endoscopy

Epidural adhesiolysis aims to release entrapped spinal nerve roots to create enough space around the nerves to restore the supply of blood and nutrients, to mechanically disrupt pain-generating scar tissue, and to facilitate spread of therapeutic substances to sites of inflammation. Although pre-adhesiolysis contrast injection may demonstrate filling defects indicative of scar tissue to guide therapy (ie steering the catheter to the side with presumed epidural fibrosis), and post-adhesiolysis contrast injection can demonstrate changes in flow patterns suggestive of successful lysis

of adhesions, one cannot visualize the contents of the epidural space or spinal canal. Spinal endoscopy has the advantage of making the epidural space visible, thus allowing the mechanical elimination of scar tissue and better evaluation of the results after injection of contrast medium.

The procedure involves the use of specialized instruments for percutaneous lysis of adhesions, often in conjunction with the use of a catheter to deliver specific therapeutic substances to promote adhesiolysis. The recommendation in the previous guideline was to perform adhesiolysis in patients with predominantly leg pain based on three RCTs.[77–79]

The evidence for adhesiolysis and spinal endoscopy in patients with PSPS-type 2 can be deduced from three systematic reviews and one additional, recently published RCT.[80–83] A systematic review of eight studies found moderate evidence for percutaneous adhesiolysis in patients with back and leg pain post-lumbar surgery or due to spinal stenosis. These studies can, however, not be compared due to the different solutions used for injection and different methods of performing the intervention.[82]

A systematic review of systematic reviews published in 2019 with a primary outcome of pain reduction (≥50%) and secondary outcomes of functional status and opioid reduction included three systematic reviews and four RCTs. The authors concluded that there is level I evidence for percutaneous adhesiolysis in patients with PSPS-type 2.[83] Geudeke et al. performed a more recent systematic review and meta-analysis of nine studies, with only two of them randomized and controlled.[80] Outcome measures included pain scores, the percentage of patients with ≥50% pain relief or satisfaction, and ODI. The seven articles with the highest quality scores were included in the meta-analysis. They found a mean VAS difference of 3.42 (95%CI 2.67–4.16) at 6 months and 2.81 (95%CI 1.60–4.02) at 12-month-follow-up. The pooled ODI mean difference was 19.42% (12.47–26.37%; 95%CI) and 19.84% (13.82%–25.86%; 95%CI) at 6 and 12 months, respectively. They concluded that adhesiolysis and epiduroscopy can be beneficial in carefully selected patients with predominantly leg pain secondary to PSPS-type 2.

In a double-blind randomized controlled study, Rapcan et al.[81] randomized 45 patients with predominantly leg pain from PSPS-type 2 into two groups. Group A was treated with mechanical lysis of scar tissue using radiofrequency, balloon inflation, or a laser plus up to 60 mL of bupivacaine and saline administered during epiduroscopy, while Group B was treated with the same protocol as group A plus methylprednisolone and hyaluronidase. They found a significant change in leg pain and function in both groups at 6 months but not at 12 months. For back pain, significant improvements were noted in both groups at 6 months, which persisted at 12 months only in group B.

Spinal cord stimulation

The field of spinal cord stimulation (SCS) was developed based on the concept of gate control theory (GCT) put forth by Wall and Melzack in their landmark 1965 article which proposed that "control of pain may be achieved by selectively activating the large, rapidly conducting fibers."[84] The first reported clinical application of SCS came 2 years later, and the field has gradually expanded since then. For nearly 50 years, since SCS was first described in 1967 until 2014, the randomized controlled trial (RCT) evidence for SCS for the indication PSPS-type 2 was limited to two trials.[6,85] The last decade has seen the emergence of many new stimulation paradigms and with these, an increase in the number of published RCTs.

SCS involves introduction of electrodes in the epidural space—either percutaneously or through laminectomy—with the purpose of the delivery of a "pulse" of current to the dorsal column to obtain neural activation. This pulse can be defined as the sustained delivery of a specific amount of current for a specific amount of time. The waveform of a pulse is characterized by one or more stimulation programs composed of a set of electrical parameters (frequency, amplitude, and pulse width), electrode configurations, and delivery patterns (continuous, burst, or clustered, cycled, or a combination). Paresthesia-based waveforms (tonic or conventional stimulation, with frequencies between 40 and 100 Hz) form the foundation of traditional SCS therapy.

Today, an estimated 50,000 spinal cord stimulators are implanted annually worldwide. The growth of neurostimulation stems in part from increasing awareness of neuropathic pain and in particular the impact of PSPS-type 2, as well as greater realization of the risks and limited benefits of chronic opioid therapy as a treatment, and the search for new strategies to avoid it. With novel stimulation paradigms, evidence is growing that SCS can be an effective and long-lasting modality for treating leg pain and back pain in carefully selected patients with PSPS-type 2.[74,86–89] Conversely, two studies with notable design flaws, discussed in several letters and editorials, have been recently published that have called into question the efficacy of SCS in patients with PSPS-type 2 and its ability to reduce opioid use in this population.[89–96]

Current evidence

All studies in the section below have included a minimal of 60% (up to 100%) of patients with PSPS-type 2 unless stated otherwise.

SCS has been shown to be an effective treatment in well-selected patients with chronic, intractable neuropathic low back and leg pain. North et al.[97] conducted the first randomized controlled trial (RCT) comparing conventional tonic SCS (<100 Hz) to repeat lumbar spine surgery in patients with PSPS-type 2. A total of 60

patients were included, with 45 patients available at 2-year follow-up. In the SCS group, nine out of 19 patients experienced at least 50% pain relief (47%) compared to three out of 26 patients in the spine surgery group (12%).[98] Kumar et al. demonstrated the superiority of tonic SCS in patients with PSPS-type 2 compared with conventional medical management (CMM). These findings were followed by the PROCESS study, a multicenter multinational RCT, which reported tonic SCS to be a viable alternative to CMM in the treatment of radicular pain in patients with PSPS-type 2.[6] An inherent flaw in these studies is that many patients were re-randomized to conservative treatments they already failed, with the expectation that they could crossover to SCS after the primary end point.

Despite these outcomes from RCTs, the overall effectiveness of traditional SCS is still limited to an approximately 50% responder rate in the long term, with up to 46.5% of patients experiencing uncomfortable paresthesia or radicular pain.[99] These forms of traditional paresthesia stimulation poorly controlled the axial component of back pain.

Other stimulation paradigms and waveforms—including high-frequency SCS (HF-SCS), burst SCS, or Differential Targeted Multiplex SCS (DTM-SCS)—have been developed with the aim of increased long-term responder rate, reduction of side-effects of SCS, and improved coverage of low back pain (LBP).

The SENZA-RCT compared HF-SCS with conventional SCS in the treatment of patients with refractory LBP and leg pain.[100] A response rate of 72%–77% after 12 months was reported with HF-SCS compared to a response rate of approximately 50% after 12 months with tonic SCS. Data from a prospective, noncontrolled, nonrandomized proof-of concept cohort study[101] suggest that the analgesia achieved with HF-SCS is durable, with 80% of patients reporting adequate pain relief at 36-month follow-up.

The SUNBURST RCT compared burst SCS to traditional SCS and reported that 70.8% of subjects preferred burst SCS over tonic stimulation at the 12-week primary end point. Improved pain reduction, defined as a decrease of daily VAS score of ≥30% from baseline value, compared to traditional SCS was also reported in this RCT.[102]

The PROCO[103] and the HALO RCTs[104] were based on the rationale that personalized electrical dosing could possibly achieve superior pain reduction, with optimal results demonstrated with the combination of a 200-Hz frequency and a pulse width of 200 ms.

The AVALON study was a prospective cohort trial that included 51 subjects with chronic leg and back pain who received treatment with a closed loop SCS system. This system uses a closed loop that automatically adjusts stimulation amplitude up to 40 times a second, assuring optimal stimulation of the cord. More than 60% of patients reported at least 80% pain relief after 6 months. Improvement in function, quality of life, and sleep quality was maintained in most patients through 24 months.[105–107]

In the EVOKE RCT and subsequent patient group analyses, open loop SCS was compared to closed loop SCS. After 24 months, closed loop stimulation was shown to provide a more consistent neural response. A 36 month data is now available demonstrating persistent long-term benefits.[108–111]

Superiority of DTM SCS compared with traditional SCS for chronic LBP was reported in an RCT, with the clinical improvement provided by DTM SCS being sustained over 12 months.[112]

In a prospective, randomized, sham-controlled double-blind crossover study, 24 subjects with predominantly axial low back pain underwent SCS therapy for PSPS-type 2. Subjects were randomized to sham, 1200 Hz, 3030 Hz, and 5882 Hz with a 4-phase crossover design over 12 weeks (frequency study).[101]

The mean low back pain score on a 10 cm visual analog scale (VAS) at baseline was 7.75. The mean VAS low back pain scores during the randomized crossover phase were 4.83, 4.51, 4.57, and 3.22 for sham, 1200 Hz, 3030 Hz, and 5882 Hz, respectively, with the lowest low back pain score observed in the 5882 Hz frequency group ($p=0.002$). Sham stimulation reduced pain by −2.92 cm (32%) and was not significantly different from stimulation at 1200 Hz and 3030 Hz.

This randomized crossover study demonstrated that 5882 Hz stimulation can significantly relieve axial low back pain compared with lower frequencies and sham stimulation. Sham stimulation produced similar analgesic effects to 1200 Hz and 3030 Hz, which may influence future neuromodulation clinical trial designs.[101,113]

Although it is tempting to propose that one frequency is superior to others, evidence is lacking to support this notion. Instead, practitioners should consider the various frequencies of SCS as different tools to treat neuropathic LBP and leg pain in individual patients, similar to how different pharmacological agents are trialed.

There is an ongoing controversy regarding the efficacy of SCS for PSPS and the effect of bias on outcomes. In a 2021 Lancet review, Knotkova et al.[114] concluded there was conflicting evidence for superiority over sham stimulation for pain reduction and quality of life, with large discrepancies observed between industry-sponsored and nonindustry-sponsored studies. In a recent investigator-initiated crossover RCT by Hara et al.,[90] the authors reported no difference between burst-SCS and placebo stimulation. In addition to evaluating an experimental mode of SCS, other limitations were discussed in several letters to the editor.[92–94,115,116]

A recent systematic review discussed the influence of industry sponsored RCTs versus physician-initiated studies. Fourteen RCTs were included with patients diagnosed with low back and leg pain, with a majority

suffering from PSPS type 2. Most of these RCTs compared new treatment algorithms (Burst, HF-10, DTM, closed loop, DRG stimulation, add on subcutaneous stimulation) with classic (traditional) tonic stimulation, with one RCT comparing high-frequency stimulation with traditional SCS.[88] The results of this meta-analysis showed improved outcomes for patients with SCS compared with patients with CMM. A clinically significant difference in pain, defined as a reduction ≥2 points on the 11 point NRS, was observed for the comparison of SCS to CMM at 6 months (pooled MD −2.51, 95%CI −3.58 to −1.45) and last follow-up (pooled MD −2.04, 95%CI −3.33 to −0.74). No differences were observed for comparisons between HF-SCS and LF-SCS.

In this systematic review, no relevant differences in outcome were noted between physician-initiated RCTs versus industry-sponsored studies. This is in contrast to a recent Cochrane systematic review of RCTs comparing SCS to placebo (sham) stimulation in which the authors found the evidence base to be dominated by industry-sponsored studies and a high rate of conflicts of interest. Table 2 lists the available evidence for interventional treatment of PSPS type 2.

COMPLICATIONS OF INTERVENTIONAL PAIN MANAGEMENT

Adhesiolysis and epiduroscopy

Complications of adhesiolysis and epiduroscopy can be both procedure- and material-related.

Pain at the needle entry site is a common feature and may be more frequent because of size of the needle required for adhesiolysis is larger than for conventional ESI. The use of excessive amounts of solutions can lead to barotrauma and ischemia of spinal nerve roots. Barotrauma and ischemia can lead to sensory and motor deficits as well as visceral and autonomic disturbances. One severe complication is retinal hemorrhage, which can occur after any epidural injection that involves high volumes and rapid rates of administration.[95]

Infection and bleeding in the epidural space can occur leading to meningitis (through inadvertent intrathecal spread), an epidural abscess, or an epidural hematoma in the case of vascular compromise. Due to high risk of neurological damage in the case of abscess and hematoma, an immediate MRI is warranted with neurosurgical consultation upon confirmation.[96,117–121]

During the procedure, needles can bend at the tip and catheters can be sheared. Catheters can be misplaced in the subdural or subarachnoid space, or rarely intravenously. Most-retained catheter fragments require periodic monitoring, though surgical intervention might be warranted depending on the location, interval movement, and patient symptoms and desires.[122] There is also a risk of dural puncture with ensuing postdural puncture headache.

Spinal cord stimulation

The most common reported side effects are loss of efficacy over time and with open stimulation, variations in stimulation parameters with postural changes. Unwanted or unpleasant stimulation is reported to occur in 2.4% of patients with tonic SCS and could lead to patient dissatisfaction or even explant surgery.[123] Similar to other surgeries, complications may occur during the placement of a spinal cord stimulator and be related to those involving surgical technique such as infections, hematoma, seroma, wound dehiscence, and skin erosion, and those involving hardware (eg lead migration, inappropriate stimulation).[58]

Infection can present as a superficial infection, a deep infection, or an epidural abscess. Superficial wound infections occur within 30 days post-implantation and involve the skin and subcutaneous tissues. Deep infections involve the IPG pocket or the lead track. Two systematic reviews report infection rates between 3.4% and 4.6%.[123,124] If a superficial infection is suspected, treatment with oral antibiotics is sufficient in most patients. If a deep infection is suspected, imaging of the epidural space is necessary to exclude the presence of an epidural abscess, and consideration of radionuclide studies to rule out or confirm hardware infection, which requires removal.[125] If an epidural abscess is present, immediate neurosurgical consultation is warranted, and surgical decompression and debridement may be indicated.

Most hematomas do not require treatment and resolve spontaneously. A seroma is a collection of fluid and its development can be mitigated by avoiding large IPG pockets and excessive tissue trauma.[58] Wound dehiscence and skin erosion are treated with debridement and primary closure in the absence of infection.

Hardware-related complications such as lead migration, lead fractures, program failures, and pain at the location of anchors and IPG pocket can occur. Pocket pain or discomfort has an incidence of up to 12%.[126] Pocket pain is typically refractory to conservative treatment such as pharmacological therapy or local anesthetic infiltration, and often requires surgical revision or explanation.[127]

Neurological damage is one of the most feared and serious complications of SCS implantation. Immediate injury can be secondary to direct needle trauma to the spinal cord and/or nerve roots or by inadvertent intramedullary placement of the SCS lead. Delayed damage can be caused by compression of the spinal cord and/or nerve roots by formation of an epidural hematoma, epidural abscess, or delayed scarring around the epidural electrode. The incidence of epidural hematoma after SCS implantation is estimated to be 0.3%.[123]

TABLE 2 Overview of the published evidence of interventional treatment of PSPS-type 2.

Author date ref	Technique	Quality of evidence	Conclusions	Recommendation
Helm 2012 Systematic review adhesiolysis	Adhesiolysis using one of the medications below: • Local anesthetic and hypertonic saline versus local anesthetic, hypertonic saline, and hyaluronidase • Hypertonic saline and hyaluronidase; hypertonic saline: isotonic saline; isotonic saline, and hyaluronidase. Adhesiolysis compared to caudal epidural steroid injection	Five RCTs and three observational studies Fair quality	Fair evidence for adhesiolysis in FBSS and spinal stenosis	Adhesiolysis with local anesthetics, hypertonic saline, and hyaluronidase can be considered for low back pain and/or leg pain post-surgery or spinal stenosis
Huygen 2019 Update of EBM guidelines	Adhesiolysis and epiduroscopy	Systematic review, RCTs, and observational studies.	Very low for adhesiolysis Moderate evidence for epiduroscopy	Very weak recommendation for epidural adhesiolysis and a weak recommendation for epiduroscopy
Geudeke 2021 Epiduroscopy for FBSS	Mechanical adhesiolysis with epiduroscopy	Two RCTs, three prospective, and four retrospective studies	Mechanical adhesiolysis by epiduroscopy can be considered and epiduroscopy could be used for the treatment of FBSS	Weak recommendation Practitioners should consider epiduroscopy after weighing the risks and benefits for individual patients with FBSS
Huygen 2019 Update of EBM guidelines	SCS for FBSS	Systematic review and RCTs and observational studies	SCS should be used in patients with FBSS	Moderate recommendation for SCS
Kurt 2022 SCS for FBSS integrative review	Integrative review SCS for FBSS	Eleven quantitative studies, seven nonrandomized, and two RCTs. Five qualitative studies	SCS positively affects different domains of life in patients with FBSS	Positive effect of SCS in different domains but limitations in daily life can persist.
Zhou 2023 SCS versus CMM chronic pain: systematic review	SCS compared with CMM alone	Four high-quality RCTs	SCS versus CMM: Improvement in pain, McGill questionnaire, QoL and disability in favor of SCS	SCS can significantly improve pain, long-term survival and quality of life, and reduce analgesic consumption. Optimization of stimulation parameters is required
Provenzano 2023 HF SCS narrative review	HF-SCS to salvage failed therapy with SCS	Three prospective and seven retrospective studies	Patients with chronic low back pain and/or leg pain experience improved and durable pain relief after conversion from t-SCS to 10 kHz SCS	Conversion from t-SCS to 10 kHz SCS can improve pain and disability More studies are needed to refine patient selection and parameters
Thomson 2017 (PROCO) Analgesia rate in kHz frequency SCS	RCT SCS with 1, 4, 7, and 10 kHz	Two patients randomized in four groups. Best setting, pulse width, and amplitude used for 5 days	There is equivalent pain relief with 1–10 kHz with appropriate titration of pulse width and amplitude	All frequencies provide equivalent pain relief 1 kHz requires significantly less current

(Continues)

TABLE 2 (Continued)

Author date ref	Technique	Quality of evidence	Conclusions	Recommendation
Deer 2017 (SUNBURST) Neuromodulation with BURST stimulation	RCT crossover Burst stimulation versus tonic stimulation	Hundred patients randomized to BURST for 12 weeks and then tonic stimulation. Follow-up for 1 year with preferred modality	Burst stimulation is superior to tonic stimulation	Burst stimulation is safe, effective, and preferable compared to tonic stimulation
Ranger MR 2008 Closed-loop SCS	RCT open-loop versus closed-loop stimulation	Sixty-seven patients with chronic refractory back and/or leg pain per group were randomized Randomized to closed or open-loop stimulation. Follow-up for 24 months	Closed-loop stimulation provided superior outcomes across all domains	Closed-loop stimulation provides improvement in patient-reported outcomes Future studies should include composite measures of holistic response

Abbreviations: FBSS, failed back surgery syndrome; HF-SCS, high-frequency spinal cord stimulation; RCT, randomized controlled trial; SCS, spinal cord stimulation; t-SCS, traditional spinal cord stimulation.

Lead migration and fractures are treated with revision, repositioning, and replacement. The reported incidence of lead migration varies from 13.2% to 27%.[126]

ALGORITHM

The algorithm for the interventional pain management of PSPS-type 2 is represented in Figure 3.

TECHNIQUES

PRF

For description of the technique for the prognostic block and PRF of the lumbar DRG, we refer to the series article on lumbosacral radicular pain.[71]

Adhesiolysis

Adhesiolysis is performed under fluoroscopic guidance with the patient positioned prone. Standard monitoring is performed with electrocardiography, noninvasive blood pressure measurement and oxygen saturation. The adhesiolysis is usually performed through the caudal canal. The average anteroposterior diameter of the sacral hiatus is about 4–5 mm, which is large enough to allow passage of a 16-gauge epidural needle. However, anteroposterior diameters as small as 1 mm have been reported.

The cornu posterior and sacral hiatus are identified and checked in a lateral view. After the administration of local anesthesia, a 16-G epidural needle is placed into the sacral canal through the sacrococcygeal membrane. Once the needle is confirmed to be in the correct position by contrast injection, a radiopaque catheter is advanced through the needle and if possible, positioned in the anterior epidural space. The C-arm is then turned to an anteroposterior view. The catheter is advanced in the epidural space until it lies at the level of the scar tissue and the affected nerve root(s). Placement is again checked by injecting contrast through the catheter, with larger volumes able to presumptively identify scar tissue by mapping the presence of filling defects. When filling defects correspond to symptoms, attempts may be made to steer the catheter toward the targeted region. After confirming correct position of the catheter, local anesthetic to promote comfort, enhance blood flow to ischemic nerve roots and suppress ectopic discharges; hyaluronidase to breakup scar tissue; hypertonic saline for possible anti-inflammatory effects and to inhibit fibrosis reformation; steroids for its anti-inflammatory and pain-alleviating properties; and contrast injection to help ascertain the technical effectiveness of adhesiolysis, are sequentially injected.[128]

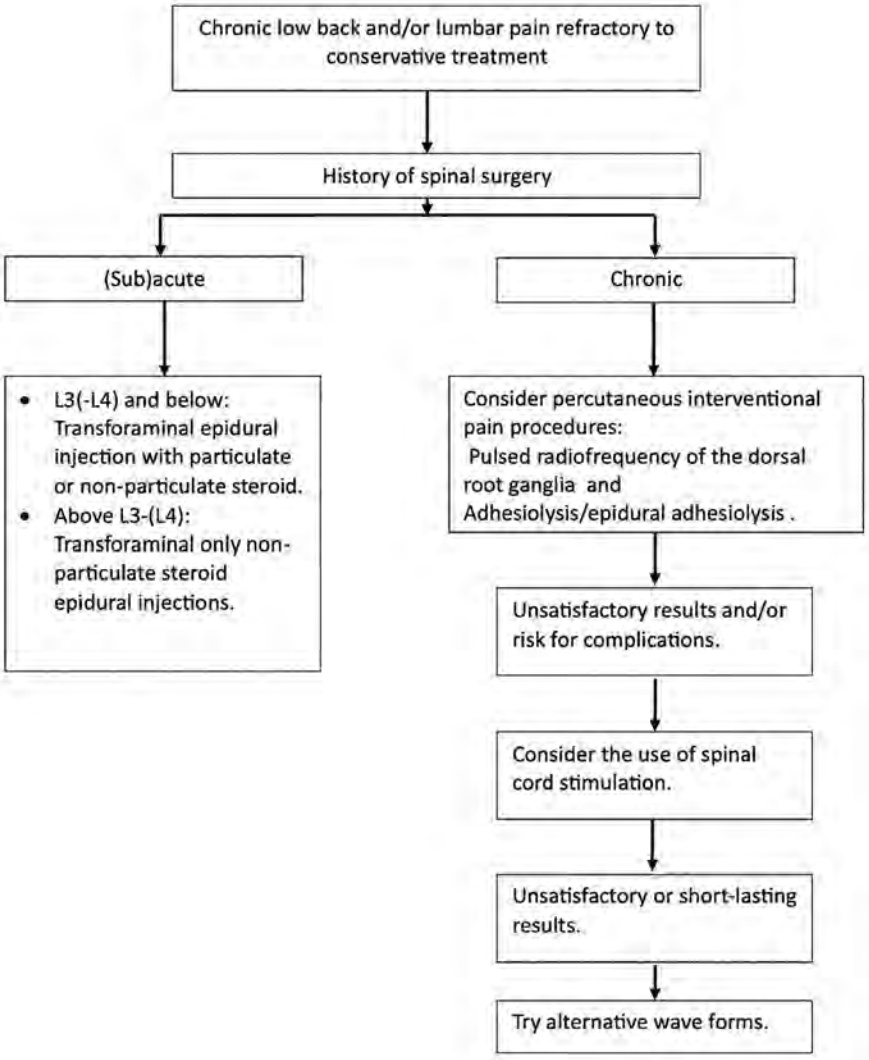

FIGURE 3 A schematic representation of the interventional treatment steps for PSPS-type 2.

Epiduroscopy

For this procedure, the patient is placed in a prone position. Standard monitoring is performed with electrocardiography, noninvasive blood pressure measurement and oxygen saturation, and intravenous access is obtained. Maintaining communication with the patient is mandatory for safety, but conscious sedation can be used.

First, the cornu posterior and sacral hiatus are identified. The skin is infiltrated with local anesthetic. Then, an 18-G Tuohy needle is placed 2 cm in the sacral canal. The S3 level is not passed to prevent dural puncture. Placement in the epidural space is confirmed by injection of contrast. When the needle is confirmed to be in the correct position, a guidewire is advanced in the epidural space to the level of L5/S1. Position of the guidewire is checked with lateral and anteroposterior fluoroscopy.

Then, the needle is removed after a small skin incision is made to facilitate the introduction of a dilator into the sacral canal. The dilator is removed, and a sheath is placed over the guidewire. The epiduroscope is then advanced through the sheath so that the epidural space can be visually examined.

Through the side ports of the sheath, saline can be delivered to remove blood or tissue from the epidural space. The epiduroscope can be steered toward suspected or visualized areas of pathology to directly target pain-generating structures. The amount of saline delivery as well as the epidural pressure should be monitored closely to prevent complications. After advancing the fiberoptic scope to the region of interest, fibrosis and adhesions can be removed mechanically.[1]

Spinal cord stimulation

Spinal cord stimulation is a surgical procedure which can be performed under local anesthesia with conscious sedation or general anesthesia. Spinal cord

stimulation generally takes place in two stages. During the trial phase, one or two leads are implanted. An incision in the skin is made typically 1.5–2 segments lower than the preconceived entry point in the epidural space. A large-bore Tuohy needle is then used to enter the epidural space using the loss of resistance technique. Needle placement and direction are confirmed using fluoroscopy.[129]

Under fluoroscopic guidance, an electrode is advanced in the posterior cervical epidural space in patients with upper limb or cervical axial pain, or to the lower thoracic region for lower limb or lumbar axial pain. The placement of the electrodes is then checked in the anterior–posterior and lateral views.

Trial stimulation can take place in the awake patient to confirm paresthesia overlap with the pain area. For high-frequency platforms, since most patients will not be able to detect stimulation, placement is confirmed empirically using fluoroscopy and pain relief with modification of stimulation patterns as necessary. After confirmation of correct positioning of the lead(s) with fluoroscopy and trial stimulation, the leads are anchored to prevent lead migration. Then a tunneling device is used to create a trajectory for extension leads through the skin. Leads are usually tunneled to the opposite side from where the internal pulse generator (IPG) will be implanted in the second stage. After placement of the extension leads, the wound is closed in layers. No tension should exist on the wound edges to minimize the risk of dehiscence and skin erosion. Sterile coverage of the surgical wound and lead extension sites is needed to prevent infection.

The second stage is performed after a positive trial period, which is defined as the achievement of at least 50% pain relief or comparable quality of life improvement during the trial phase. During the second stage, a pocket is created in the gluteal or abdominal area to fit the IPG. The wound in the back is reopened to remove the extensions. After cutting the extensions, the leads should be removed. The leads are next tunneled to the pocket and inserted into the IPG. Before wound closure, a final check for the connections is made by measuring impedances. After confirmation, wounds are closed in layers. For an extensive review on surgical technique in SCS, we refer readers to the NACC guidelines.[129]

CONCLUSIONS AND RECOMMENDATIONS

Epidural corticosteroid injections and pulsed radiofrequency treatment adjacent to the dorsal root ganglion can be considered, with low-to-moderate evidence supporting their use for radicular pain. Future studies specifically in patients with PSPS-type 2 are warranted.

There is low-quality evidence for percutaneous adhesiolysis and epiduroscopy in the treatment of patients with PSPS and predominantly leg pain, with benefits also reported for axial pain. These treatments can be considered in well-selected patients in specialized centers.

In carefully selected patients with PSPS and predominant leg pain and patients with predominantly back pain who have failed conservative therapies and respond well to a trial, SCS can be an effective treatment with a moderate level of evidence supporting its use.

AUTHOR CONTRIBUTIONS

Johan van de Minkelis performed the literature search. He and Laurens Peene reviewed the literature. Johan van de Minkelis wrote the article and Laurens Peene revised it. S. P. Cohen, P. Staats, and A. Al-Kaisy provided additional references and comments, they also edited the article, JW Kallewaard provided additional references and comments, he also edited the article; J. Van Zundert controlled the article, provided comments, and has full responsibility for the end product.

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