Success Rates and Safety in Managing Spinal and Sacro-Iliac Pain: A Critical Analysis

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1. BACKGROUND

1.1 Symptomatology

1.1.1 Low back pain (LBP)

Low back pain (LBP) or lumbar spinal pain is a common problem, showing an estimated global point prevalence of 18.3%, 1-year 38%, and lifetime 42% in the general population; the point prevalence is consistently higher in females than in males at all ages, while the difference is not significant for 1-year and lifetime prevalence, and it peaks between 40 and 80 years of age [1]. Moreover, LBP is the leading cause of years lived in disability in high- and middle-income countries, although a specific source of pain cannot be identified in 90-95% of cases [2].

Often, LBP resolves spontaneously without specialized treatment, and it is classified into three categories: acute (> 4 weeks), subacute (4-12 weeks), and chronic back pain (> 12 weeks), the latter experienced by 4-25%, or even up to 40%, of patients with LBP [2,3]. The most frequent and relevant factors leading to chronicity are higher pain intensity and body weight, physical jobs involving lifting heavy weights or uncomfortable positions, functional limitations in acute episodes, depression, anxiety, and smoking, whereas general good health, consistent physical activity, and, surprisingly, higher blood pressure are protective factors [2]. Individuals suffering from chronic back pain experience a significant decline in their quality of life; they exhibit reduced functional capacity, lower levels of physical activity, alterations in their psychological well-being, and mood disorders such as depression, anxiety, and sleep disturbances [2,4].

The etiology of LBP can be categorized into mechanical (aching or dull pain), neuropathic (sharp or burning pain), systemic (inflammatory), or secondary to other causes (visceral or neoplastic); however, in the majority of cases a cause is not identified (nonspecific back pain) [3]. Specific mechanical causes may include conditions such as joint, bone, or disc degeneration (osteoarthritis), traumas, spondylolysis/spondylolisthesis, scoliosis, kyphosis; neuropathic ones are due to spinal or nerve root compression by herniated disc, annular fissure, or spinal stenosis (radiculopathy). Other causes include inflammatory forms of arthritis, infections, neoplasms, referred visceral pain, fibromyalgia, or psychosomatic disorders [3].

1.1.2 Neck Pain

Neck pain is the fourth leading cause of disability in the US; the adult population shows a point prevalence ranging from 5.9% to 38.7%, and the 1-year prevalence in the elderly population is approximately 10%. Females report neck pain more frequently than males. The most common causes are inadequate ergonomics at work, like sitting and maintaining neck posture in a non-physiologic position for long periods of time [5]. Acute episodes of neck pain typically resolve in weeks or months, faster with physical therapy and a hard collar, though pain and/or functional alterations may linger or recur, and like for back pain, the origin may be musculoskeletal or neurological, for compression of spine or nerve roots (radiculopathy), most often for facet joint spondylosis or herniation of an intervertebral disc [5,6]. Cervical radiculopathy is defined as a

syndrome of pain and/or sensorimotor deficits due to compression of a cervical nerve root, and it can manifest as arm pain or paresthesias in the dermatomal distribution of the affected nerve, possibly associated with neck pain and motor weakness [6].
Muscle relaxants like cyclobenzaprine may be more helpful for neck pain relief than non-steroidal anti-inflammatory drugs (NSAIDs), while epidural corticosteroid injections, combined with adjuvants and physical therapy, are more effective than each treatment alone; in addition, nerve radiofrequency ablation can successfully treat zygapophyseal joint pain [5]. Surgery should be performed only in case of sudden (trauma) or progressive neurological deficits for spine or nerve compression [5,6].

1.1.3 Thoracic pain

Thoracic spine pain is defined as pain experienced between the boundaries of T1–T12 and across the posterior aspect of the trunk [7]. The thoracic spine is a common site for inflammatory, degenerative, metabolic, infective and neoplastic conditions (including osteoporosis, vertebral fractures, hyperkyphosis, ankylosing spondylitis, osteoarthritis), which may also contribute to pain and disability. However, thoracic pain has been studied less extensively than cervical and lumbar pain, and mostly among children and adolescents, as associated with backpack use, showing extremely wide ranges of point prevalence, due to variable definitions, outcome measures, and periods considered (4-72%) [7]. Data are also inconsistent about its prevalence and burden in the adult population; several studies report a 1-month prevalence < 10%, and 1-year prevalence ranging between 15% and 35% [7].
The source of this pain should be carefully examined, as it may be referred pain from thoracic or abdominal organs with various pathologies. Spinal pain may originate from the nerve endings of the periosteum, intercostal nerves, ligaments, intervertebral discs, facet joints, or vertebral fractures, or secondary to thoracic surgery; it could be nociceptive (paravertebral, diffuse) or neuropathic (along dermatomes) [8]. Thoracic radicular pain most commonly originates from a disc herniation (particularly lateral), degenerative stenosis, or vertebral compression fracture; it is often associated with axial pain, and the majority of thoracic disc herniations are below the T8 level [9]. The diagnosis could be confirmed with selective nerve blocks of intercostal nerves or dorso-medial branches of the segmental nerves for facet joints; non-surgical pain management could be performed conservatively or through radio-frequency ablation of spinal nerves or root ganglions [8]. In case of disc herniation or spinal stenosis, epidural steroid injections could also be performed, via transforaminal (TFESIs) or interlaminar (ILESIs) routes, with variable effectiveness [9,10].

1.2 Causes

1.2.1 Spine osteoarthritis

Osteoarthritis (OA) affects the appendicular and axial skeleton. OA is typically seen as a ‘whole joint disease,’ since all joint structures (cartilage, bone, synovium, and muscles) can be affected

by the disease, which is characterized by cartilage degradation, bone remodeling, osteophyte formation, and local inflammation [11]. Mechanical stress is considered to cause remodeling of the joint, possibly producing an imbalance between destruction and repair, ultimately leading to joint failure, manifesting with pain, stiffness, and functional limitations [11]. The joints involved may include knees, interphalangeal, hips, and facet joints of the lumbar and cervical spine; OA of the lumbar facet joints has pathologic and clinical characteristics similar to appendicular OA [12]. Lumbar spine OA is very common, with estimates of prevalence ranging from 40–85% [13]. The process of OA degeneration of the spinal facet joints (the only synovial joints in the spine) appears secondary to intervertebral disc alterations, commonly occurring with age, although no consensus has been reached across several studies, with others finding stronger associations of pain with disc narrowing than OA [13]. Facet joint OA has been correlated with the symptom of back pain even before compression of neural structures, though the actual pain source for some patients appears to be inflammation of the inner articular structures, and for others the outer capsule and its innervation, and it is possible to differentiate between the two only with diagnostic nerve blocks [12]. The different origins can partly explain the widely different effectiveness of some treatments like intra-articular steroid injections or radiofrequency ablation of the nerves [12].

1.2.2 Lumbar canal stenosis

Central spinal canal narrowing is considered the primary characteristic of lumbar canal stenosis, though the specific degree of narrowing causing neurological symptoms is variable. A study has been conducted to establish a connection between a narrowed spinal canal and clinical symptoms, and found that small dural sac cross-sectional area, morphological grading, and negative sedimentation sign (failure of the spine/cauda equina to move inferiorly in the prone scanning position) based on magnetic resonance imaging (MRI) are significant indicators of spinal stenosis as opposed to simple back pain, although they do not correlate significantly with the disability index provided by the patient [14].

Lumbar spinal stenosis is a common and debilitating source of lower back and leg pain among older individuals, with a prevalence of approximately 11% in the adult US population, increasing with age [15]. Most cases can be treated conservatively, with physical therapy, oral medications, or epidural steroid injections, whereas surgery can be performed on carefully selected patients with pain resistant to other treatments [15]. The diagnosis is typically established based on the patient's history of back and leg pain, exacerbated by back extension and alleviated by flexion, confirmed with imaging tests like computed tomography (CT) or MRI [15].

1.2.3 Neuroforaminal stenosis

Neuroforaminal stenosis is another significant cause of debilitating pain due to lumbosacral radiculopathy, with a reported incidence of 8-11% [16]. Central spinal stenosis, caused by disc herniation or idiopathic, may compress one or more nerve roots or the whole spinal cord, whereas foraminal stenosis impinges the root exiting the spinal space through the osseous foramen between two vertebrae, affecting the blood supply and inducing inflammation [16]. It presents with pain in

the low back (typically in the glutes) and leg (dermatomal distribution), with possible focal motor weakness, reduced sensations, or absent reflexes, exacerbated by back extension, and it can be confirmed with radiographic studies, static or in lumbar extension, CT, or MRI (modality of choice), particularly with 3D reconstructions [17].
Several factors may contribute to foraminal stenosis. The most common causes include decrease in the adjacent disc height, impinging facet joint synovial cysts, redundant facet joint capsule, facet arthropathy, ligamentum flavum hypertrophy, degenerative or iatrogenic anterolisthesis, and osteophytes [17]. In addition to physical therapy and oral analgesics, it can be treated with transforaminal steroid injections [16,18] or surgery.

1.2.4 Discopathy

Degeneration of intervertebral discs, or discopathy, is one of the causes of LBP. However, the correlation between discopathy severity and LBP remains unclear. A 2023 study reported that the number of levels affected by discopathy is associated with the age and body mass index (BMI) of the patients, but it was not correlated with the pain intensity, the lumbar spine's range of rotational motion, or the functional status of the patients, though the latter association approached significance [19].
With age, the intervertebral disk may lose hydration, and the nucleus is compressed, damaging the outer annulus; if this structure ruptures, the nucleus may infiltrate the fissure and protrude into the spinal canal, compressing the spine or nerve roots, causing pain, weakness, numbness, or changes in sensation. Most disk herniations occur in the lower lumbar spine, especially at L4-L5 and L5-S1 [20].

1.2.5 Lumbar radiculopathy and sciatica

Sciatica, a specific manifestation of lumbar radiculopathy, refers to pain that radiates along the path of the sciatic nerve, the main nerve of the lower limb. When the sciatic nerve or one of its roots is affected, it can cause varying pain levels, from a mild ache to a sharp, burning sensation, and may also be accompanied by numbness, tingling, or muscle weakness in the affected leg [21].
Sciatica is a common spinal condition with high reported lifetime prevalence (1.2–43%, depending on different definitions) and is most commonly caused by lumbosacral disc herniation [22]. The most common causes of LBP with sciatic radiation are: lumbar intervertebral disc hernia, lumbar spinal stenosis (in the elderly population), spondylolisthesis (vertebral antero-posterior misalignment), pelvic or lumbar muscular spasm and/or inflammation, spinal or paraspinal mass (54).
Epidural steroid injections can provide significant leg pain relief and functional improvement in patients with sciatica. Caudal and transforaminal injections in particular provide better leg pain relief than interlaminar injections, and patients with radiologically confirmed lumbar disc herniation benefitted more than clinically diagnosed patients. A meta-analysis reported strong evidence for the effectiveness of lumbar epidural injections with local anesthetic and steroids, and

moderate-to-strong evidence for local anesthetic alone in managing lumbar radiculopathy or sciatica secondary to lumbar disc herniation [23].
Occasionally, back and leg pain with the characteristics of sciatica originate from the hip joint instead or in addition to sciatic pathology, e.g., in osteoarthritis (OA); a study reported concurrent hip pathology in approximately 25% of cases [24]. Hip OA is a leading cause of global disability, with limited effective non-surgical treatment options, and should be considered in the differential diagnosis.

1.2.6 Sacroiliac joint dysfunction

Sacroiliac joint dysfunction (SIJD) refers to pain or discomfort in the sacroiliac joints, which connect the sacrum to the ilium bones of the pelvis. The diagnosis of SIJD can be challenging due to the complex anatomy of this region and symptoms overlapping with other spinal disorders. However, detailed history taking, pain location, gait patterns, and provocative maneuvers, in addition to careful imaging assessment, can aid in its diagnosis [25]. Several risk factors have been associated with the development of SIJD, including pregnancy, trauma, previous lumbar fusion surgery, arthritis, scoliosis, and abnormal gait patterns [26]. Treatment strategies for SIJD typically involve a multidisciplinary approach, including physical therapy, manual therapy, exercise programs, and in some cases, intra-articular injections of corticosteroids or PRP, radiofrequency ablation, or surgery [27]. However, the efficacy of these treatments remains variable, and more research is needed to establish optimal management strategies for SIJD [26]. Interestingly, there is a higher rate (i.e., up to 40%) of SIJD being the source of low back pain in patients with failed back surgery syndrome (FBSS) with the rate in some studies noted as high as 63% [28].

1.3 Non-surgical management of lumbar radiculopathy

Initial treatment for lumbar radiculopathy should focus on conservative management, including patient education, exercise, physiotherapy, massage therapy, aqua therapy, McKenzie exercises, topical creams (NSAIDs), muscle relaxants, anti-spastics, and other analgesics or physical therapies. McKenzie exercises [29] and oral corticosteroids may provide short-term relief. If these measures are inadequate, local injections (epidural, into facet joints, or transforaminal) can offer long-term relief. These injections, combining an anti-inflammatory agent and a long-lasting anesthetic, can also help localize the pain source [30].

1.3.1 Treatment options

Non-surgical treatments include the modification of daily activities, such as reducing the time spent standing or walking, various types of physical or psychotherapies, and topical or oral medications (NSAIDs, gabapentinoids, baclofen, duloxetine, and opioids for resistant pain [31], and possibly ketamine [32] or low-dose naltrexone [33]). The evidence on long-term benefits of epidural steroid injections for lumbar spinal stenosis is currently inconsistent [15,34].
Some medications such as naltrexone are used off-label to help patients with chronic back pain and other types of neuropathic pain [35]. Naltrexone is mainly used to reduce dependency of

alcoholics or narcotics. At regular dosage, naltrexone is a high-affinity reversible competitive antagonist of the μ-opioid receptor, whereas at low doses it increases opioid signaling with a transient rebound effect after opioid receptors blockade. Typically, it is well tolerated with only mild side effects; however, the effective dose can vary widely between patients, and the effects can be noted only after a month or longer, making titration difficult [36]. Nonetheless, its use is expanding, and research is ongoing.

The pharmacological treatment for LBP is divided into three main categories: oral medications (such as NSAIDs, opioids, anticonvulsants, muscle relaxants, and antidepressants), topical medications (capsicum, piroxicam, and lidocaine creams), and spinal injections (epidural for radiculopathy, intra-articular for facet and sacroiliac joint pain, and intradiscal for short-term pain relief) [31].

In addition, LBP can be caused by musculoskeletal issues beyond the spine, such as the sacroiliac joint (SIJ), hip OA, and greater trochanteric pain syndrome (GTPS). In developed nations, SIJD stands out as the most common cause of LBP, comprising 15-30% of cases [25]. GTPS is often associated with central spinal stenosis and OA of the lumbar spine, hip, and knee, and its prevalence varies by sex, with women experiencing it more frequently than men (23.5% vs. 8.5%) [37].

1.3.2 Spinal steroid injections

One of the most common management options for patient with LBP is corticosteroid injections to reduce inflammation and pain. The injections are administered into the lumbar epidural space through interlaminar, transforaminal, or caudal approach. Initially, these injections were performed as a treatment for radiculopathy, first described in 1901, via caudal route, using cocaine or local anesthetics. Steroids were added to the injections in the 50s, and the interlaminar approach was subsequently introduced. In the late 1990s, the transforaminal approach was developed to deliver the medication directly to the presumed site of pathology [38,39]. These injections are generally effective, though with variable results [23].

Caudal epidural steroid injections are a common therapy for individuals experiencing LBP and radiculopathy of the lower lumbar or sacral vertebrae. Administered into the sacral hiatus at the base of the sacrum, these injections aim to alleviate inflammation and pain resulting from conditions such as a herniated disc or other lumbosacral spine issues [20]. Research has commonly shown that caudal epidural steroid injections are successful in managing chronic LBP, although they may not offer prolonged relief in every instance [20,40,41]. For improved accuracy and safety, this procedure can be performed under imaging guidance using fluoroscopy (FL) or ultrasonography (US) to ensure the needle enters the epidural space to prevent complications during injection. The success rate of blind caudal epidural injections in adults is reportedly 74-90%, but it increases to 85-100% with US- or FL-guided approach [42]. Post-operative outcomes, in terms of pain relief and complication rates, showed no significant differences in safety and efficacy between different guidance techniques, though FL-guided injections offer slightly

improved efficacy on the patients' functionality, whereas US has the advantage of no radiation exposure, lower costs, and convenience for patients and doctors [42].

Interlaminar epidural injections, on the other hand, can deliver the injectate directly into the epidural space of the whole spine, inserting the needle between the laminae of two neighboring vertebrae. This interventional pain management technique is utilized in the cervical, thoracic, or lumbar spine to target specific areas of discomfort, and the injectate usually consists of a blend of anesthetics and steroids. The interlaminar approach allows a multilevel spread of the medication, offering particular benefits to patients with spinal stenosis involving several vertebrae [43]. A study comparing caudal and lumbar interlaminar injections with local anesthetics and steroids showed in patients with chronic nonspecific LBP showed no significant differences in efficacy at 6, 12, and 24 months [44].

Transforaminal injections target specific areas, including the anterior epidural space (AES), dorsal root ganglion, and single nerve roots, to reduce inflammation, delivering the injectate into the vertebral foramen, where the nerve root emerges from the spine. FL guidance with contrast enhancement provides precise real-time images to prevent injury to critical vessels and accidental intravascular or intrathecal injections [45]. Reviews of randomized controlled trials (RCTs) and meta-analyses have supported the safety of FL-guided transforaminal injections, showing minimal serious complications [38]. However, there is a concern regarding increased radiation exposure of patients and medical staff during real-time FL or digital subtraction imaging (DSI). As for caudal injections, over the last decade US has emerged as a reliable method to guide transforaminal injections, offering several advantages over traditional radiologic methods. US provides improved visualization of soft tissues and vascular structures in anatomical regions, while also avoiding the use of ionizing radiation [42].

Facet joints, also known as zygapophysial joints, are diarthrodial articulations between the posterior elements of adjacent vertebrae. Facet joints provide stability and mobility, allowing the spine to bend and twist. These joints have innervation from the medial branches of the dorsal rami of the spinal nerves, and each segmental branch supplies two homolateral facet joints, superiorly and inferiorly, thus each joint is innervated by two branches. Lumbar facet joint pain may radiate to the back, buttocks, and proximal lower extremities [46,47]. Intraarticular facet joint injections, facet joint nerve blocks with local anesthetics, or facet joint neurolytic procedures are popular for the management of facet joint pain, often caused by OA; moreover, intra-articular facet joint injections and nerve blocks have diagnostic value. They have the advantages of a simple technique and localized containment of the infiltrate within the joint; however, their efficacy depends on the adequate diffusion of drugs into the joint capsule. Intraarticular facet joint injections and facet joint nerve blocks should be performed ideally under FL guidance [46,47]. Alternatively, US guidance showed comparable results for safety and efficacy [48].

A possible long-term side effect associated with repeated corticosteroid injections is the decrease in bone density in postmenopausal women, with consequent increase in pathological fractures [39,49]; therefore, steroids should be administered with caution and in limited doses in this population. However, the results are inconsistent.

2. RATIONALE

Spinal pain in the lumbar, thoracic, and cervical regions is a prevalent and multifaceted issue that significantly burdens the healthcare system. Steroid injections, including caudal epidural, transforaminal, and interlaminar approaches, are targeted therapeutic interventions designed to deliver corticosteroids with anti-inflammatory effects directly to the affected area. This method is particularly effective in managing spinal pain by addressing the underlying pathology while minimizing systemic exposure and associated side effects.

However, these injections lack a standardized protocol regarding patient selection, route of administration, local anesthetic, type of steroid, dosages, length of follow-up, number and frequency of repeated injections, and other details. This proposal seeks to investigate and optimize the use of steroid injections in spinal pain management, aiming to refine treatment strategies for this widespread and challenging condition, and also to examine their safety and possible long-term side effects. We will also examine results for specific genes included in a targeted pharmacogenetic panel in a subset of patients to explore potential mechanisms contributing to interindividual variability in drug efficacy and/or tolerability.

2.1 Overview of the study

2.1.1 Study design

This single-centre study will consist of two parts, one retrospective and one prospective with cross-over design, to analyze and summarize our experience in the evaluation of:

- Efficacy of US-guided epidural steroid injections (caudal and interlaminar, compared to transforaminal if performed elsewhere and data available) in patients with lumbar-sacral pain for central spinal stenosis, neuroforaminal stenosis, herniated disc, or FBSS;
- Efficacy of cervical, thoracic, and lumbar facet joint and SIJ injections in patients with nociceptive spinal pain (e.g., OA);
- Spinal levels most frequently affected;
- How frequently a pain presenting as sciatica is actually due to hip OA, trochanter pain, bursitis, or SIJ pain, rather than spine pathology.

In this study, we will include at least 100 patients per part with lumbar spinal pain due to lumbar canal stenosis, herniated discs or FBSS (lumbar radiculopathy), treated with caudal and interlaminar epidural steroid injections through different protocols, all under US guidance. In addition, we will examine different administration protocols include the following injections: facet joints (100 each for cervical, lumbar, and thoracic) and/or SIJ (100), compared with injections of local anesthetics only, with Marcaine or Sensorcaine (bupivacaine) or Xylocaine (lidocaine), or oral low-dose naltrexone (spinal radiculopathy).

2.1.2 Aim

Comparing these interventions through rigorous research, we can provide healthcare professionals with refined treatment guidelines, optimized patient care pathways, and ultimately improve

outcomes and quality of life for those living with back pain. This research will benefit current patients and contribute to the broader knowledge in pain management, guiding future advancements in the field.

2.1.3 Objectives

The primary objectives of this study are to determine:

- The short-term pain relief response: the difference between pre- and post-treatments based on numeric rating scale (NRS) scores at 1 and 2 weeks;
- The long-term pain relief response, by examining the results of pain relief expressed as magnitude (percentage) and duration (in days) in patients receiving different injections, combined in the integral of pain relief (IPR) scores (IPR = percentage of relief * number of days), and the patient's global impression of change (PGIC, a 7-point word scale describing the improvement or worsening of pain after a treatment), after 4, 6, 8, and 12 weeks, and at 6 and 12 months if possible;
- The patient's functional disability pre- and post-treatment at the same time points with the PROMIS Physical Function and Pain Interference/Intensity tool and functional IPR (fIPR), for more or less detailed different grades of improvements. The fIPR will be obtained as a measure of overall improvement in daily functioning (e.g., walking, hygiene, housekeeping, ability to work or study, fatigue, sleep, mood, leisure), as a percentage, and its duration. The degree of pain interference with daily activities, on a scale from 0 to 10 or percentage, will also be examined.

The secondary objectives of this study are to assess:

- Differences in efficacy between different types and doses of steroids and between steroids and local analgesics only;
- The types, number, and severity of side effects;
- Potential genetic mechanisms underlying variable responses to four corticosteroids (and the respective doses employed) in terms of both efficacy and safety/adverse reactions. Variations in CYP3A4 will be examined, as it is responsible for an established metabolic pathway common to all four agents. Additionally, variations in a related metabolic gene CYP3A5 and the drug transporter gene ABCB1 will also be explored as they both have considerable substrate overlap with CYP3A4.
- The effect of different injection locations (caudal or interlaminar, central or directed to the affected side) on pain relief, including the reduction rate of opioid or other medications, like medical or recreational cannabis;
- Independent variables that may impact efficacy and safety of pain relief, including:
    - age, sex, BMI, occupation, duration of chronic pain (years), anticoagulant medications, chronic kidney disease (CKD, stage 2-4), hypertension, diabetes, osteoporosis, fibromyalgia, cataract, glaucoma, smoking and alcohol consumption, post-surgery period, advanced age (> 90 years);

- The history of pain medications and their change after the injections;
- Bone mineral density (BMD) before and after steroid injection (if available) to examine the hypothesis of injectable steroids reducing bone density and posing a risk for osteoporosis;
- Safety and efficacy of oral low-dose naltrexone in patients who are eligible to receive this medicine (in doses of 1-9 mg, with effects usually noticeable after 1-3 months of use), of different types and doses of steroids in patients who received epidural or intraarticular injections, and of lidocaine infusions for LBP in patients with sciatic pain;
- Frequency of sciatic, SI joint, IT bursa, trochanteric, and hip joint pain in patients with LBP;
- Validity of fIPR to evaluate patients with spinal pain and their functionality, with possible differences due to pathogenesis/localization (stenosis, disc herniation, facet joints and SIJ OA);
- The possible influence of changes in body weight on the treatment efficacy of ultrasound guided injections or pain in general;
- Prognostic value or meaning of the feeling of pressure on the leg during the injection, as reported by some patients.
- Other potential sub-analysis of different factors that may emerge as relevant.

3. STUDY SITE AND POPULATION

3.1 Study site

The principal investigator (PI), Dr. Igor Wilderman, MD, is specialized in chronic pain management and procedural medicine. He is the medical director of Wilderman Medical Clinic and the director of the Canadian Centre for Clinical Trials. Dr. Wilderman is also disciplined in advanced biostatistics and research methods. The co-investigator, Dr. Alexander Shenderey, MD, FRCPC, is a certified anesthesiologist, also specialized in procedural medicine. He is a staff anesthesiologist at Brampton Civic Hospital and a pain physician and anesthesiologist at Wilderman Medical Clinic. The study team will also include Francesca Sarzetto, MD MSc, research analyst with extensive experience in medical and clinical research, and Rukhsar Gul (PA, MPAS) for patient recruitment and communications.

All research will be conducted at Wilderman Medical Clinic, a chronic pain clinic located near the intersection of Yonge St. and Hwy 7 in Thornhill, Ontario. The clinic consists of state-of-the-art facilities, an interdisciplinary team, nursing support and coordination, and on-site lab. In addition, our clinic has experience with conducting retrospective chart review studies [50,51], prospective investigator-initiated studies [52,53], and conducting industry-sponsored clinical trials as part of the Canadian Centre for Clinical Trials.

3.2 Study Population

The participants will be recruited from Wilderman Medical Clinic. For the retrospective part of the study, the patients meeting inclusion criteria and who signed the informed consent for research analysis will have their electronic medical records (EMR) accessed for chart review.

3.2.1 Inclusion criteria - Part 1

To be included in Part 1 of the study, patients must fulfil the following criteria:

- > 18 years of age;
- Diagnosed with lumbar, cervical, or thoracic pain with various etiologies;
- Received one or more steroid injections for back pain, including epidural, facet joints, or SIJ injections; or other injections (e.g., local anesthetics);
- Provided NRS pain rating immediately before the intervention and at least one after the intervention (between 2 weeks and 6 months);
- Had follow-up data recorded;
- Provided written informed consent to access and analyze their data for research purposes.

3.2.2 Exclusion criteria - Part 1

Patients will be excluded from Part 1 of the study based on the following criteria:

- Diagnosis of dementia, Parkinson's disease, or other cognitive impairments, unless information is available from next of kin;
- Congenital or acquired polyneuropathy;
- Any other medical condition that may interfere with the study assessments.

3.2.3 Inclusion criteria - Part 2

Patients will be recruited for the prospective part of the study if they meet the following criteria:

- >18 years of age;
- Diagnosis of lumbar, cervical, or thoracic pain with various etiologies;
- Eligibility to receive steroid injections for back pain, including epidural, facet joints, or SIJ injections, or other injections (e.g., local anesthetics);
- Being willing and able to provide NRS pain ratings and PROMIS functionality ratings before the intervention, and the same scores plus IPR, fIPR, and PGIC at various follow-up points after the intervention;
- Provide written informed consent.

3.2.4 Exclusion criteria - Part 2

Patients will be excluded from the study based on the following criteria:

- Diagnosis of dementia, Parkinson's disease or other cognitive impairments;
- Congenital or acquired polyneuropathy;
- Back surgery in the month before injection treatment or planned surgery in the subsequent 3 months;

- Any clinically significant acute or chronic medical condition that in the judgment of Investigator may preclude injection in the epidural space or compromise patient safety, limit patient's ability to complete the study, and/or compromise the objectives of the study;
- Participation in any other competing clinical study within 3 months prior to screening and during the study period.

4 STUDY PROCEDURES

4.1 Protocols

4.1.1 Part 1 - Retrospective

The first part of the study will follow a single-centre, retrospective chart review design. This part will be conducted on approximately 100 male and female patients who were diagnosed with lumbar radiculopathy for epidural injections and 100 or more each for cervical, thoracic, lumbar facet joints and SIJ injections.

A non-blinded reviewer will access medical charts with the following OHIP diagnostic and medical procedure codes:

- LBP (code 724) or cervical, thoracic spinal pain (code 847);
- FBSS (codes 724 and E441);
- Caudal epidural steroid injections (procedure code G918);
- Interlaminar epidural injections (procedure code G246).

Patients will be selected for analysis in the study when treated with various types and doses of US-guided injections:

- Caudal epidural injections (20, 40, or 80 mg Kenalog [triamcinolone], or Depo-Medrol [methylprednisolone], or Celestone [betamethasone], or dexamethasone in equipotent doses);
- Interlaminar epidural injections (same medications);
- Facet joint injection (4 mg or 8 mg Kenalog or other steroids in equipotent doses);
- SIJ injection (8, 16-20 mg Kenalog or other steroids in equipotent doses);
- Only local anesthetics.

Different protocols applied to the same patient at different times will be used to compare efficacy and safety of the injections with a cross-over design. Information regarding the clinically relevant outcomes will be obtained from chart review. De-identified data will be stored in a password-protected database.

The patient's response to treatment will be assessed through NRS and PROMIS scores, recorded before and after the injection, along with PGIC, duration and percentage of pain relief, combined in the IPR, and functional improvement (fIPR) recorded during the follow-up visits.

The patient demographic and medical data regarding their age, sex, occupation, duration of chronic pain (years), presence of diabetes or other comorbidities, BMD (if available), use of medical or recreational cannabis, opioids, or other pain medications, smoking, and alcohol consumption will be retrieved from the charts, added to the password-protected database, de-identified, and analyzed in agreement with the statistical analysis plan.

4.1.2 Part 2 - Prospective

The second part of the study will be a cross-over prospective study. A total of approximately 100 patients per arm, as above, will be recruited for participation in the study, and the recruitment will be performed by in-person appointment. First, all participants will undergo one or two different diagnostic local anesthetic facet joint and/or SI injections with bupivacaine, lidocaine, or ropivacaine. Those participants who had a positive result of the diagnostic injections will each undergo one or two different injection protocols for steroid type, administered via either caudal or interlaminar epidural injections (by Dr. Wilderman or Dr. Shenderey, respectively), facet joint or SIJ injections, all US-guided, with the same steroids as above in selected cases, depending on the specific pathology. Patient who had significant relief (> 50%, lasting > 4 weeks) after injection of local anesthetics will be offered to have subsequent injections with the same anesthetics, either alone or with the addition of a steroid. The order of the different steroids will be randomized, and each will be started with the lowest dose; if one effectively provides > 25% additional pain relief lasting over 4 weeks, the injection will be repeated with a double dose of the same steroid to examine possible further improvements; other steroids will be administered during the following visits at the equipotent dose as the one that provided the greatest pain relief based on the IPR.. The steroid will be changed up to three times in subsequent injections to determine which one provides the greatest benefit for that patient, with intervals of approximately 2 months. The decision whether to double the dosage or change steroid will mostly rely on the patient's feedback, though the goal is to provide at least 25-50% pain relief for a period of 6-8 weeks or longer. If the addition of steroids does not lead to improved outcome compared to local anesthetics, the patient will continue treatments with local anesthetics only. The injections will not be administered during follow-up visits if the patient has ongoing relief from the previous one.

Fifty patients will be selected to evaluate if a standard midline caudal epidural injection provides the same relief as right or left-sided (the side most affected by sciatica symptom). These patients will receive 1 midline and 1 right- or left-sided injection in a cross-over way. We will use the optimal dose and the best steroid as per each patient response.

Each patient will be evaluated with NRS (average, min, and max, at rest or with activity) and PROMIS scores at baseline (and for BMD in about 50% of patients, as clinically indicated), and with the same scales plus IPR, fIPR, and PGIC at follow-ups, by phone or in person, for a total of 4-8 weeks, plus or minus 1 week, following an injection. The efficacy will be evaluated at six or seven time points (baseline, week 1, 2, 4, 6, 8, and 12 post-treatment evaluations, if applicable), plus 6 and 12 months. These data will also be used to validate the IPR and fIPR as measures of efficacy of treatments for chronic pain in the cervical and lumbar spine (we anticipate that the number of patients with only thoracic spine pain will be insufficient), after we validated the IPR for steroid injections in knee osteoarthritis [53].

In addition, a subset of approximately 50 patients with diverse ethnic backgrounds and clinical characteristics will be selected for a pharmacogenetic study, whereby a targeted set of genes will be analyzed by Inagene (Inagene, Inc. Toronto, ON, Canada) to determine the presence of

variations that may contribute to different responses to the four corticosteroids. Moreover, we plan to analyze changes in BMD in a subset of patients who receive steroid injections for at least a year, with a second densitometry examination 12 months or longer after the first injection, to investigate the possible correlation with type and/or dosage of steroid.

4.2 Different types of injections

4.2.1 Caudal epidural steroid injections (Dr. Wilderman)

The patient is placed in the prone position (lying face down) on the procedure table. Alternatively, the patient can be positioned in a lateral decubitus position (lying on one side) if they cannot lie prone comfortably. A pillow or bolster may be placed under the pelvis to slightly flex the hips and flatten the lumbar lordosis, making it easier to access the sacral hiatus. A high-frequency US linear transducer (7-15 MHz) is typically used for imaging superficial structures like the sacral hiatus and surrounding tissues. The US machine is positioned on the side of the patient for easy access and visualization during the procedure. The transducer is placed longitudinally over the sacrum, just above the gluteal cleft. The sacral cornua and sacral hiatus are visualized as landmarks. Then, the transducer is rotated and placed transversely and tilted slightly, showing the sacral hiatus as a hypoechoic (dark) gap between the two hyperechoic (bright) sacral cornua. The caudal canal appears as a hypoechoic tubular structure below the sacral hiatus. Under continuous US guidance, a small gauge needle (typically 22-25G) is inserted at a 45-degree angle to the skin. Usually, we use a 2-inch needle. The needle is advanced slowly towards the sacral hiatus, visualized in real-time as it approaches and enters the hiatus. The needle tip is carefully advanced into the caudal epidural space. If necessary, the transducer can be rotated longitudinally to better visualize the needle trajectory. Once the needle is assumed to be in the correct position, a small amount of normal saline or local anesthetic may be injected under US visualization. The spread of fluid within the caudal epidural space can be seen as an anechoic (dark) area expanding in the targeted space. This helps confirm that the needle is correctly positioned in the caudal epidural space. After confirming the needle placement documented with picture or videos, the corticosteroid (e.g., triamcinolone, betamethasone, or dexamethasone) mixed with a local anesthetic (e.g., lidocaine or bupivacaine or ropivacaine) and normal saline (20 mL in total) is injected slowly into the caudal epidural space. US or US-Doppler can be used to monitor the distribution of the injectate and ensure it spreads adequately within the epidural space [54].

4.2.2 Interlaminar epidural injections (Dr. Shenderey)

An 18G, 3.5-inch or 4-inch Tuohy needle will be advanced into the posterolateral epidural space of the side of the leg affected with radicular symptoms, using the loss-of-resistance technique under US guidance. This “directed lateral interlaminar approach” may improve the delivery of the injectate to the site of the pathology without increasing the technical difficulty or side effects of the procedure. Using loss of resistance technique and after negative aspiration for cerebrospinal fluid and blood, a combination of 20-40 mg of methylprednisolone acetate or equipotent steroid with 0-3 mL of lidocaine 1%, plus saline solution for a total volume of 8-10 mL, will be injected into the epidural space [55].

4.2.3 Facet joint injections separately for cervical, thoracic, or lumbar spine (+ SIJ)

Patients will be placed in a prone position. Paravertebral sagittal sonograms will be obtained to identify the different spinal levels. The spinous process and adjacent structures (lamina of the vertebral arch, facet joint, accessory process, and mamillary process) will be delineated by transverse sonograms at the target level, and the midpoint of the facet joint space will be established. All procedures will be performed under sterile conditions. If the joint is clearly or partially visible, a spinal needle will be advanced under US guidance into the joint space of each lumbar facet joint. The needle will be inserted 1-2 cm laterally from the midline at the lateral end of the transducer and precisely positioned in the US plane at an angle of approximately 45° with respect to the axial plane until the needle tip reaches the target and bony contact is felt. This will enable visualization of the needle, which will appear as a bright line-shaped echo pattern on the transverse sonogram. If the needle placement is correct, a mixture containing steroid and local anesthetic in a volume of 0.6-1.0 mL will be administered intraarticularly (until resistance is encountered) per joint as needed and into the area surrounding the posterior facet joint capsule [48].

4.2.4 Sacroiliac injections with lumbar facet joints

In the sacroiliac joint injection procedure with ultrasonography, the patient is positioned prone on the examination table, ensuring comfort and accessibility to the sacral region. To improve access and visualization of the SIJ, a small bolster may be placed under the patient's pelvis to slightly flatten the lumbar lordosis. Once the area is sterilized, the clinician applies a low-frequency linear US transducer over the sacral area, specifically targeting the region over the sacroiliac joint. The joint appears as a hypoechoic (dark) line between the hyperechoic (bright) sacrum and ilium, which serve as a guide for needle placement. Local anesthesia is then administered subcutaneously to numb the skin and underlying tissues, ensuring patient comfort during the procedure. Under continuous US guidance, a 22-25G spinal needle is carefully inserted and directed toward the SIJ space. The needle's advancement is closely monitored on the US screen, allowing the clinician to make real-time adjustments to ensure accurate placement within the joint. Once the needle is confirmed to be in the correct position, a small amount of saline or anesthetic may be injected to verify the spread within the joint space. This helps confirm the needle's placement before the therapeutic injection. The injection itself consists of a mixture of a corticosteroid and a local anesthetic, such as bupivacaine (0.25% or 0.5%) or lidocaine (1-2 mL). This combination is slowly injected into the sacroiliac joint under US visualization, ensuring proper distribution of the medication within the joint space. Using US guidance for SIJ injections enhances the precision and safety of the procedure, making it a valuable technique in managing SIJ pain [56].

5. OUTCOME ASSESSMENT

5.1 Part 1 – Retrospective: cross-over design with up to three same-steroid, same-dose interventions per patient and up to four different ones

The information to be collected includes age, sex, occupation, presence of diabetes, CKD, fibromyalgia, or other comorbidities, use of medical or recreational cannabis, opioids, and other pain medications, smoking, and alcohol consumption; NRS and PROMIS scores at baseline and follow-ups, and at follow-ups also dimensions of the IPR (percentage and duration of pain relief) and fIPR (percentage and duration of functional improvement), when available. Patient names and other identifying information will not be attached to the data. Many patients have already been treated in our clinic with several injections, and we can combine the data on effectiveness for the same type or different ones for steroid type or dose.

5.1.1 Numeric rating scale (NRS)

The NRS is a standardized, one-dimensional measure of pain intensity, rated by the patient using a scale from 0 to 10, with 0 being "no pain" and 10 "the worst pain imaginable." The NRS score is a widely used, reliable, and validated measure of pain intensity, which can be used at a single time point (usually as the average of the previous 24 hours) or recorded daily for prolonged periods, to obtain an overall mean value or to follow the progression of pain in time [57].

5.1.2 Integral of pain relief (IPR) and functional IPR (fIPR)

The IPR is a multidimensional measure, combining the percentage of pain relief provided by the treatment multiplied by its duration in days, divided by 100. The IPR aims to provide a more comprehensive understanding of the treatment efficacy, since it is an estimate of both the decrease in pain intensity and the period covered, without relying on continuous monitoring of the pain intensity or only the current level at any pre-specified time. The scale has the number of days since the intervention as maximum value (multiplied by one in case of complete relief, or fractions corresponding to the percentage of relief) and 0 as minimum (no treatment effect). Therefore, the higher the IPR value, the more effective the treatment was at reducing pain [52].
The fIPR is a similar index evaluating the percentage of general functionality improvements, again multiplied by the number of days covered.

5.1.3 PROMIS

PROMIS-29 is a questionnaire with 29 questions evaluating the general status of a patient in the previous 7 days, each with scores from 1 (never or with no difficulty) to 5 (always or unable to do). The questions are grouped in section for physical function, anxiety, depression, fatigue, sleep quality, social participation, pain interference with various life aspects (four items each), and the final question for pain intensity with the NRS score (0-10).

5.2 Part 2 - Prospective

The information to be collected will be the same as in Part 1. In addition, the patients will be asked to provide another value, not previously collected: the patient's global impression of change

(PGIC). This is a simple, 7-grade ordinal scale (from 1 to 7), describing the general change perceived by the patient, from 1-Very much improved to 7-Very much worsened, with 4 being "No change." This value will be collected at each follow-up for an easier interpretation of the patient's experience, and those who give a PGIC value of 1 or 2 will be considered responders to the treatment.

5.3 Statistical considerations

Various descriptive statistics (sample size, mean, standard deviation and confidence intervals, or median, interquartile ranges, minimum, and maximum in case of non-normal distribution of the data) will be calculated on the patient population for continuous variables. The normality of data will be assessed using the Shapiro-Wilk test for frequentist statistics. Frequencies and percentages (with corresponding confidence intervals) will be presented for categorical and ordinal variables.
The initial analysis will compare the efficacy and safety of different routes of epidural injections, both with short-term and long-term responders, using the Chi-square test to compare the observed proportions, and ANOVA or similar tests to compare means of NRS, IPR, fIPR, and PROMIS values. All statistical tests used will be two-sided and p-value less than 0.05 will be considered statistically significant. ANOVA will also be used for pharmacogenetic testing, or ANCOVA, as appropriate, controlling for possible variables that may influence the pharmacokinetics/dynamics of steroids, such as other drugs, liver or kidney dysfunction, history of organ transplant.
General linear models and logistic (or linear) regression models will be used to assess responders in relation to several variables, adjust for demographic and clinical factors, and compare efficacies of different injections routes. Model selection will be performed by stepwise reduction from the full model until the overall model strength is maximized as assessed by the likelihood ratio. The Hosmer-Lemeshow test of model fit of the logistic model will be used to test for lack of fit. Odds ratios and 95% confidence intervals will be calculated. The latest version of SPSS will be used for all analyses.

6. DESCRIPTION OF RISKS AND BENEFITS

6.1 Possible risks

6.1.1 Part 1

This part of the study is a retrospective chart review, with no direct patient interaction involved and no risks for the patients.

6.1.2 Part 2

Caudal and interlaminar epidural injections and facet joint and SIJ injections are routinely performed by certified physicians (IW and AS), with the support of qualified nurses, as part of regular treatments at the Wilderman Medical Clinic. All possible risks and side effects of the treatments are listed in the patient's informed consent form to the injections, read and signed by

patients before every treatment. The risks associated with participating in the study for patients who regularly receive such injections in the clinic are considered relatively low.

6.2 Possible benefits

Epidural and other injections can offer several potential benefits for patients with LBP:

- **Pain Relief:** One of the primary benefits is pain relief. These injections can help reduce inflammation and swelling surrounding the spinal nerves, often leading to a significant reduction in pain.
- **Improved Function:** By reducing pain, the patients may experience improved function and mobility. This can allow individuals to participate in physical therapy and other activities that may have been difficult due to the pain.
- **Avoiding Surgery:** For some patients, the injections can provide sufficient relief to avoid surgery. This is particularly beneficial for those who want to explore non-surgical options first or those who may not be good candidates for surgery.
- **Diagnostic Tool:** In addition to providing pain relief, the injections can serve as a diagnostic tool. If a patient experiences temporary relief from the injection, it can help confirming the source of the pain, aiding in further treatment planning.
- **Long-Term Relief:** While the duration of pain relief varies from patient to patient, some individuals experience long-term benefits from the injections, providing an extended period of improved quality of life and functionality.
- **Combined with Other Therapies:** Different types of steroid injections can be part of a comprehensive treatment plan, including other therapies such as physical therapy, oral medications, and lifestyle modifications.

Sharing these findings can serve as a valuable tool for clinicians to choose the most suitable injection procedure for each patient. Furthermore, it can assist in establishing optimal dosages, treatment schedules, expected duration and magnitude of pain relief, as well as factors that may impact treatment efficacy.

7 INFORMED CONSENT

7.1 The consent process

7.1.1 Part 1

Most patients provided written consent for Wilderman Medical Clinic to anonymously analyze demographic and medical information contained in their virtual charts. The patients of Wilderman Medical Clinic are informed about the research nature and purpose of medical chart reviews, as well as participation and termination conditions, potential risks, and benefits.

7.2.2 Part 2

Prior to the recruitment for the study and the initiation of any related procedures, the patients will be asked for their written consent to participate in the study. The consent process will take place in a quiet, private area before any procedures. A designated staff member will describe the nature

and purpose of the study, participation and termination conditions, as well as risks and benefits. The potential participant will be given time to review the document and ask questions. The informed consent form will be signed and dated and the participant will be provided with a copy of the document.

7.2 Consent documents

The Canadian SHIELD Ethics Review Board will examine the informed consent documents (general and for the genetics part from Inagene) and other documentation before the initiation of the study. A copy of the informed consent will be provided to the patient. If applicable, it can be translated and certified. The signed consent forms will remain in each patient's study file, available for verification by study monitors at any time.

7.3 Participant withdrawal

Participation in this study is voluntary. Each patient will be informed of their right to withdraw their consent and interrupt their participation at any time for any reason and without prejudice. The reasons for any patient's withdrawal will be documented and reported. The participants will be informed that any data collected until withdrawal may be used in the final analysis, if feasible.

8. CONFIDENTIALITY

8.1 Confidentiality of data

All the medical information obtained by this study is confidential and will not be disclosed to any third parties. Following CIHR's best practices for protecting privacy in health research, de-identified data will be stored in a secure, password-protected database, accessible only to study personnel, for 25 years, after which it will be destroyed.

8.2 Data security, retention and access

The PI will adhere to the protocol as detailed in this document and agrees that any changes to the protocol must be approved by the research ethics board. The PI will be responsible for enrolling only those patients who have met protocol eligibility criteria.

All data will be stored on a password-protected electronic medical record system on a password-protected server. No identifying information will be attached to the extracted data. Access to data will be restricted to Dr. Wilderman and his research team. All the information collected during the course of the research will be kept strictly confidential. Data will be further cleared of any identifying descriptors before addition into the database for analysis. No information in these records about the identity of the patients will leave the clinical site. The confidentiality of all patient records will be maintained.

At Inagene (pharmacogenetic study), a separate register will store the participants' data with anonymized identifiers, and only the sex will be retained for quality control.

9. STUDY OVERSIGHT

This study may be prematurely terminated at the discretion of the PI. The protocol, informed consent documents, and relevant supporting information will be submitted to the IRB for review and must be approved before the study is initiated. In addition, any subject recruitment materials will be approved by the IRB before being used. This study will be conducted following the ethical principles that have their origin in the Declaration of Helsinki and are consistent with good clinical practice (GCP) and applicable regulatory requirements. The PI will submit any change to the protocol to the IRB for review and approval before implementation.

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