REVIEW ARTICLE

Regenerative Medicine for Axial and Radicular Spine-Related Pain: A Narrative Review

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■ **Abstract**

Introduction: Regenerative injection-based therapy has established itself as a therapeutic option for the management of a variety of painful musculoskeletal conditions. The aim of this work was to review the current literature regarding regenerative injection therapy for axial/radicular spine pain.

Methods: A comprehensive literature review was conducted on the use of regenerative medicine for axial/radicular spine pain. Eligible articles analyzed the therapeutic injection effects of platelet-rich plasma (PRP), prolotherapy, or mesenchymal signaling cells (MSCs) via intradiscal, facet joint, epidural, or sacroiliac joint delivery.

Results: Regarding intradiscal PRP, there are level I/IV studies supporting its use. Regarding intradiscal prolotherapy, there are level III to IV studies supporting its use. Regarding intradiscal MSCs, there are level I/IV studies supporting its use with the exception of one level IV study that found no significant improvement at 12 months. Regarding facet joint injections with PRP, there are level I/IV studies supporting its use. Regarding facet joint injections with prolotherapy, there are level IV studies supporting its use, though the one level I study did not demonstrate any statistical significance supporting its use. Regarding epidural injections with PRP, there are level I/IV studies supporting its use. Regarding epidural injections with prolotherapy, there are level IV studies supporting its use, though the one level I study did not demonstrate statistical significance beyond 48 hours. Regarding sacroiliac joint injections with PRP, there are level I/IV studies supporting its use. Regarding sacroiliac joint injections with prolotherapy, there are level I/III studies supporting its use.

Conclusions: Currently, there are level I studies to support the use of PRP and MSC injections for discogenic pain; facet joint injections with PRP; epidural injections of autologous conditioned serum and epidural prolotherapy; and PRP and prolotherapy for sacroiliac joint pain. One level I study showed that facet joint prolotherapy has no significant benefit. Notably, no intervention has multiple published level I studies. ■

Key Words: orthobiologics, prolotherapy, platelet-rich plasma, mesenchymal stem cells, medicinal signaling cells, regenerative medicine, back pain, radicular pain

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INTRODUCTION

Over the past decade a proliferation of treatment options under the titles of orthobiologics, regenerative medicine, and interventional orthopedics have become

available. Due to the specific nature of these therapies, the wide array of treatment options, and the lack of insurance coverage, it remains difficult to report epidemiological data accurately. For pain of spinal origin, they are becoming more routinely available and include platelet-rich plasma (PRP), bone marrow concentrate, prolotherapy, mesenchymal signaling cells (MSCs), and other biologic signaling factors. Their increasing use in the treatment of spinal pain is being driven by 2 main factors. Through word of mouth and anecdotal stories from peers, certain patients may be skeptical of conventional treatment's ability to provide durable, long-term relief. The second factor is the search for nonsurgical, holistic, and "natural" remedies to promote self-healing. Historically, there has been a paucity of high-quality peer-reviewed evidence for orthobiologic use. However, this is changing as orthobiologic treatments come to the forefront with the emergence of well-designed trials published in recent years.

Pain originating from the spine, especially pain poorly responsive to "standard of care" treatment modalities, has long posed challenges for healthcare providers and the greater healthcare system at large. Axial spine pain has been reported at least since the dawn of modern history, having even been described by Hippocrates in his book *On the Articulations*.[1] The problem remains substantial since "back problems" are the leading cause of years lived with disability and the third most prevalent reason for ambulatory office visits.[2,3]

The high incidence of back pain places an enormous economic burden on the healthcare system. Dieleman et al.[4] found between 1996 and 2013 healthcare spending on low back and neck pain increased the second most compared to 155 other medical conditions. The average adjusted medical cost per year is $3,600 greater for those with low back pain, and increasing resources are being allocated to its treatment and diagnosis, with estimated expenditures increasing by 65% from 1997 to 2005.[5] Unfortunately, despite expenditures increasing by 8% per year, the levels of chronicity and disability associated with low back pain continue to rise. Clearly, back pain is a growing financial healthcare burden.

In light of the growing cost, incidence, and prevalence of people experiencing chronic back pain, alternative and improved treatment options have been a major point of emphasis.[6] One major treatment, opioid analgesics, has been proven to be ineffective for management of these types of injuries, and has led to a healthcare crisis in its own right. According to the Centers for Disease Control and Prevention (CDC), use of prescription opioids has quadrupled since 1999; however, the amount of self-reported pain in the United States has remained unchanged.[7] The CDC also reported that opioids accounted for over 47,000 deaths in 2017.[8] Additionally, given the current opioid misuse epidemic, the CDC recommends significant caution in opioid prescribing for chronic noncancerous pain management and offers extensive guidelines regarding best practice when there is a decision to prescribe.[9]

Another common treatment modality for many musculoskeletal conditions is corticosteroid injections. However, there are limitations to this treatment with regards to frequency and duration of effect, and a growing body of literature demonstrates the potential teno-toxic and chrondro-toxic properties associated with these injections.[10] In general, the use of interventional pain procedures has increased enormously over recent years (a 228% utilization increase from 2000 to 2011), and Medicare paid over $2 billion dollars for them in 2006 alone.[11] The largest increase was for facet joint interventions at 386% and sacroiliac joint (SIJ) blocks at 310%, but other techniques such as epidural injections (186%) and percutaneous disc procedures (28%) also saw a rise.[11]

In addition to these more routine treatments, there exists a multitude of other treatment options for spine-related pain. Orthobiologic therapy is an alternative treatment option in the multimodal management of pain.[12] As new treatment modalities emerge, it is a medical and ethical necessity to continually review and assess the available literature for the effectiveness of available therapies. This narrative review aims to assess the currently available literature as it relates to the use of orthobiologics for the treatment of axial spine and radicular pain disorders. For the purpose of this review, these disorders included all studies addressing zygapophyseal joint, discogenic, and radicular pain ranging from the cervical to lumbar spine, as well as SIJ pain.

EPIDEMIOLOGY

Pain originating from the spine is incredibly common, with an annual point prevalence of 13% for chronic low back pain and 4.9% for neck pain.[13,14] The overall prevalence is likely higher than reported as this pain is best documented in high-income populations, with limited data from their middle- and lower-income counterparts.[15] The most common pain generators in the lumbar spine are the intervertebral disc and

zygapophyseal, or facet, joints. Up to 50% of low back pain in patients treated at specialized pain or orthopedic clinics is alleged to be of discogenic origin, while facet joint–mediated pain may account for another 33%.[16,17] In the cervical spine, facet joint–mediated pain predominates and has been estimated to account for 40% to 60% of non-neuropathic neck pain.[18] Age plays a significant factor as low back pain is rare in children before they reach school age and rises in prevalence until 18 years of age, when it matches adult rates.[19] In addition to nociceptive spine pain, there exists radicular pain. Radicular pain is pain radiating along a nerve root without neurologic involvement. This differs from the typical nociceptive pain in that the axons are stimulated from the perinevrium and not the peripheral nerve terminals.[20] Colloquially this is often called neuropathic pain. Prevalence of neuropathic low back pain has been reported at approximately 5%.[21]

METHODS

A comprehensive literature review was conducted on the use of regenerative medicine for axial spine and radicular pain. The following electronic databases were used for the search: PubMed, Google Scholar, and The Cochrane Library. Searches were performed for each orthobiologic agent: PRP, prolotherapy, and MSCs. PRP search terms were: "platelet-rich plasma" OR "PRP" AND "discogenic" OR "disc" OR "facet" OR "epidural" OR "radicular" OR "sacroiliac". Prolotherapy search terms were: "prolotherapy" AND "discogenic" OR "disc" OR "facet" OR "epidural" OR "radicular" OR "sacroiliac". MSC search terms were: "bone marrow aspirate concentrate" OR "BMAC" OR "adipocyte signaling cell" OR "ASC" AND "discogenic" OR "disc" OR "facet" OR "epidural" OR "radicular" OR "sacroiliac".

Eligible articles were written in English and analyzed the therapeutic injection effects of PRP, prolotherapy, or MSCs via intradiscal, facet joint, epidural, or SIJ delivery on human patients diagnosed with spine-related pain. PRP, prolotherapy, and MSCs were the 3 orthobiologic agents chosen to include within this review because they are the most common agents used for regenerative injection-based therapy in musculoskeletal medicine and are the most well studied.[22] Exclusion criteria were case reports and studies in which spine-related pain was not the principal diagnosis. Three authors (D.R., J.T.M., B.M.) screened the titles and abstracts to identify potentially eligible studies. If an article was not immediately excludible from its abstract, a full text review was performed. Out of the initial 239 articles, 35 met the inclusion criteria and were included in this review. The primary outcomes for most studies were pain or disability. Details regarding the study search are included in Figure 1.

ORTHOBIOLOGICS AND THE LITERATURE

Description of Orthobiologics

The American Academy of Orthopedic Surgery describes orthobiologics as "the use of biological substances to help musculoskeletal injuries heal quicker. They are used to improve the healing of fractured bones and injured muscles, tendons and ligaments and are derived from substances that are naturally found in the body. When they are used in concentrations many times the normal, they can potentially help speed up the healing processes."[23] Commonly, these injections are composed of cells, scaffolding, and growth factors. The most common orthobiologics administered for the treatment of musculoskeletal pain are PRP, prolotherapy, and MSCs. MSCs primarily consist of bone marrow aspirate concentrate (BMAC) and adipose signaling cells (ASCs). In this section, we review their proposed mechanisms of action and thus why they are emerging as promising treatment options for pain.

Platelet-Rich Plasma

PRP consists of an autologous concentrate of platelets made from centrifugation of whole blood to increase platelet concentration with the removal of other cellular components. For efficacy, the platelet concentration must be higher than baseline. The proposed mechanism for PRP as a therapeutic is that PRP initiates the body's own repair processes, modulates inflammation, delivers growth factors, and attracts and activates mesenchymal stem cells, which promote a healing environment and reduce pain.[24] In vitro studies have shown PRP to induce downregulation of the crucial inflammatory molecules interleukin-6 (IL-6) and IL-8, which can help attenuate hyperalgesia.[25]

Preparation standardization has been recommended to better guide clinical application, and the PLRA (platelet count, leukocyte presence, red blood cell presence, and activation) classification system described by Mautner et al.[26] provides the most current comprehensive classification system. PRP injections can be

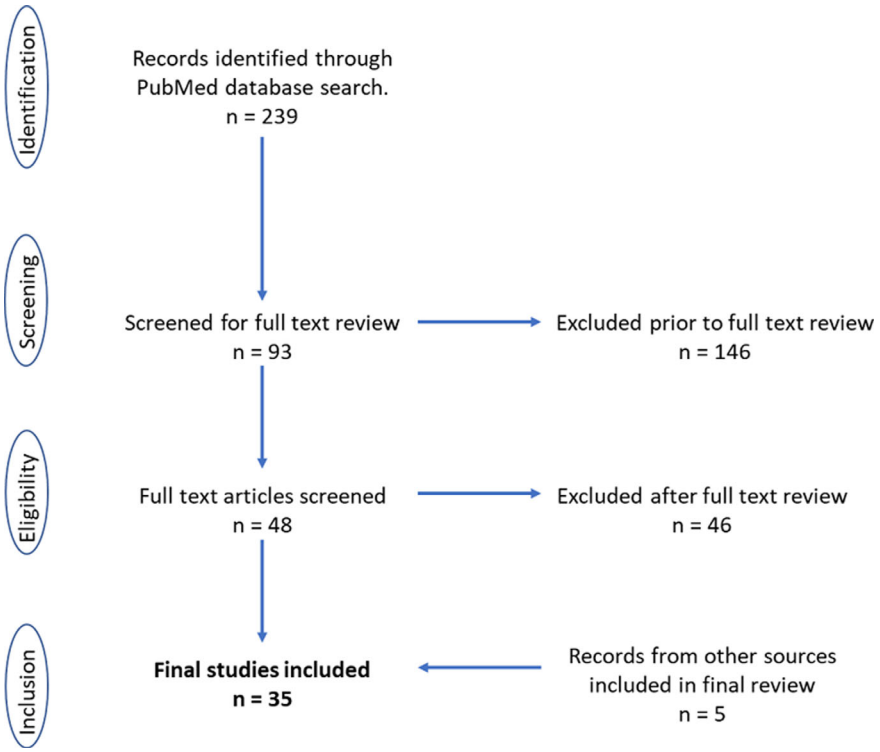

Figure 1. Flowchart of study inclusion.

performed at the point of care and with a low rate of adverse events.

Prolotherapy

Prolotherapy involves an injection of a solution not containing biologic material with the goal of repairing connective tissue and ameliorating pain. Most commonly, hypertonic dextrose is used, but phenol and sodium morrhuate have been described as well. These 3 proliferants represent the different classes of prolotherapy: osmotic agents, irritants, and chemotactic agents, respectively. Irritants damage cell membranes, and chemotactic agents are thought to directly induce the inflammatory cascade. Osmotic agents cause local tissue irritation, leading to recruitment of inflammatory cells, which may trigger a healing cascade.[27] Dextrose is the most well studied and is viewed as the ideal proliferant because of its water solubility and ability for safe injection into multiple areas.[28]

Mesenchymal Signaling Cells

MSCs are cells with the perceived capability to proliferate and differentiate into cells that regenerate tissue functionality following injury.[27] They are perivascular in origin and can be isolated from any vascularized tissue.[29] Initially described to be present in bone marrow by Dr. Alexander Friedenstein, these regenerative cells have now also been shown to be present in peripheral blood, skeletal muscle, and adipose tissue. In vitro studies have shown these cells to express growth factors such as transforming growth factor beta (TGF-β) and vascular endothelial growth factor, which are known to stimulate local tissue repair.[30] Additionally, they suppress the proliferation of inflammatory T-cells and inhibit monocyte maturation, creating both immunomodulatory and anti-inflammatory effects.[30,31] Their ability to decrease inflammation and promote tissue repair has sparked an increase in their usage for the treatment of musculoskeletal pain. Most commonly, bone marrow aspirate and fat transfer techniques are used in regenerative medicine.

Bone Marrow Aspirate Concentrate. Bone marrow aspirate concentrate is the term used to describe the MSCs and marrow elements obtained from bone marrow aspiration. The posterior iliac crest is most commonly used, since it has been shown to provide the highest concentration of MSCs.[32] The aspirate must

undergo density gradient centrifugation to isolate progenitor cells because they account for a small population of the cells within bone marrow (0.001% to 0.01%).[33] BMAC has been shown to serve as a source for growth factors such as platelet-derived growth factor, TGF-β, and bone morphogenetic protein 2, which have anabolic and anti-inflammatory effects.[34] Bone marrow–derived platelets included in BMAC differ from those of peripheral blood used in PRP and have been shown to provide additional growth factors and potentially aid chondrogenesis.[35,36]

Adipose-Derived Signaling Cells. Adipose-derived signaling cells (ADSCs) are MSCs that have been isolated from homogenized adipose tissue through lipo-aspiration. Adipose tissue provides an excellent medium for MSC harvest secondary to its abundant vasculature. The procurement procedure consists of a minimally invasive harvest with higher cell concentration per unit volume and less susceptibility to culture expansion senescence compared to BMAC. Numerous mechanisms have been proposed to explain how ADSCs may support repair and help regenerate tissues. As described previously, secretion of cytokines and growth factors through a paracrine mechanism likely play a large role. Pagani et al.[37] demonstrated in vitro that ADSCs had higher matrix composition and gene expression compared to BMAC that may improve chondrogenic potential in an inflammatory environment. Release of free radical scavengers and antioxidants elicited from ADSCs may promote cell survival and help remove toxic substances, which could help mediate the inflammatory response.[38]

Orthobiologic Treatments for Axial Spine and Radicular Pain: Current Literature

Here we provide the available literature on regenerative medicine therapeutics for treating spine-related pain categorized via injection delivery location: intradiscal, facet joint, epidural, and SIJ. Levels of evidence for each study were determined by the criteria of the American Association of Physical Medicine and Rehabilitation, an adaptation of those proposed by *The Journal of Bone and Joint Surgery*.[39]

- Level I—Randomized controlled trials or systemic review of level I randomized controlled trials.
- Level II—Prospective cohort studies, poor-quality randomized controlled trials, systemic reviews of level II studies, or non-homogenous level I studies.
- Level III—Case-control studies, retrospective cohort studies, systemic reviews of level III studies.
- Level IV—Case series.
- Level V—Expert opinion.

Discogenic Orthobiologic Studies

Table 1 outlines the relevant discogenic orthobiologic studies culled from the literature.

PRP. Table 1a summarizes the characteristics and results of the currently available studies regarding intradiscal PRP. There was only one level I study and multiple level IV studies on the effects of intradiscal PRP. Through a double-blind randomized controlled trial, Tuakli-Wosornu and colleagues demonstrated that intradiscal PRP vs. an Omnipaque 180 contrast control provided significant improvement at 8 weeks regarding pain and function. Results were sustained at 1 year for the PRP group, but notably comparative outcomes vs. control were not evaluated after 8 weeks.[40] Four additional studies analyzed PRP, and one analyzed autologous leukocyte-reduced PRP outcomes.

Regarding prospective trials, the results were positive for PRP, with pain outcomes improving in the majority of PRP-treated patients.[41,42] Notably, the Comella et al. study used a combination of stromal vascular fraction (SVF) and PRP for their injectate; SVF is a combination of ADSCs and growth factors. The remaining prospective PRP study found 47% of patients had a greater than 50% improvement in VAS scores and a 30% decrease in Oswestry Disability Index (ODI) scores at 6 months.[43]

Kirchner et al.[44] performed a retrospective observational study utilizing 1 facet joint, 1 intervertebral disc, and 1 epidural injection of autologous leukocyte-reduced PRP in 86 patients with chronic low back pain and found significant improvements in VAS scores, with 91% reporting an "excellent" score. Of note, all 3 targets were injected in the same visit. Additionally, Navani et al. performed a case series in which patients received either intradiscal PRP or BMAC-MSCs. This study found 93% of patients achieved a reduction of greater than 50% in their verbal pain scale (VPS) scores at 18 months. It is noteworthy that there was no distinction regarding which or how many patients received PRP vs. BMAC-MSC.[45]

Table 1. Discogenic Orthobiologic Studies—(a) PRP; (b) Prolotherarpy; (c) MSC

Author (Year)	Level of Evidence	Study Details	Composition	Results	Pain Outcome Measures
(a) PRP					
Tuakli-Wosornu et al.[40] (2016)	I	Design: prospective double-blinded RCT Intervention: PRP vs. contrast control Sample size: 47 [29 PRP] Follow-up: 12 months	P: 3 to 4 mL L: NR R: NR A: NR Control: 3 to 4 mL Omnipaque 180 contrast agent	Significant improvement in PRP group at 8 weeks regarding pain (NRS), function (FRI), and satisfaction (NASS Outcome Questionnaire). At 1 year PRP group had significant improvements in NRS worst pain, FRI, and SF-36 pain (outcomes vs. control not evaluated after 8 weeks).	NRS SF-36 Pain
Akeda et al.[41] (2017)	IV	Design: prospective clinical feasibility study Intervention: PRP Sample size: 14 Follow-up: 10 months	P: 2 mL 907 × 10^3/μL L: – R: + A: + ($CaCl_2$)	Significant improvement in VAS at 1 month that was sustained through follow-up of ~10 months	VAS
Navani et al.[45] (2018)	IV	Design: case series Intervention: PRP or BMAC-MSC ×1, 1 to 3 discs Sample size: 15 Follow-up: 18 months	P: 1 to 2 mL L: NR R: NR A: – BMAC-MSC: 1 to 2 mL	>50% relief in VPS in 94% of patients at 6 months and in 93% of patients at 18 months. SF-36 physical component summary was improved in 100% of patients at 6 months and in 93% of patients at 18 months. Medication use decreased in 89% of patients at 6 months and in 80% of patients at 18 months.	VPS SF-36
Kirchner and Anitua[44] (2016)	IV	Design: observational retrospective pilot study Intervention: 1 intradiscal, 1 intra-articular facet, and 1 transforaminal epidural injection of PRGF-Endoret Sample size: 86 Follow-up: 6 months	P: 4 mL (2× peripheral blood) L: NR R: NR A: + PRGF activator ($CaCl_2$)	After PRGF injection to intervertebral disc, transforaminal epidural injection, and facet joints, significant improvements in VAS scores were obtained, with 91% of patients showing an excellent score, 8.1% with moderate improvement, and 1.2% with lack of response.	VAS
Levi et al.[43] (2016)	IV	Design: Prospective trial Intervention: PRP ×1, 1 to 5 discs Sample size: 22 Follow-up: 6 months	P: 0.5 to 1.5 mL L: + R: NR A: NR	Success determined by 50% or greater improvement in VAS and 30% decrease in ODI. Categorical success rates were as follows: 14% at 1 month, 32% at 2 months, and 47% at 6 months.	VAS ODI
Comella et al.[42] (2017)	IV	Design: open label Intervention: PRP/SVF ×1, 1 + discs Sample size: 15 Follow-up: 6 months	SVF (ASC + GFs) plus: P: 1 mL L: NR R: NR A: NR	Statistically significant improvement in VAS, PPI, SF-12, and flexion at 6 months. Additionally, both ODI and BDI data were trending positive and a majority of patients reported improvements in their Dallas Pain Questionnaire scores.	VAS, PPI, ODI, and SF-12
(b) Prolotherapy					
Miller et al.[47] (2006)	IV	Design: prospective case series Intervention: bi-weekly hypertonic dextrose (average 3.5 injections) Sample size: 76 Follow-up: 18 months	50% dextrose	33 (43.4%) achieved sustained improvement, with an average improvement in NPS of 71% at 18 months. 37 (48.7%) nonresponders (<20% pain reduction); 6 temporary (<2 months) responders.	NPS
Derby et al.[46] (2004)	III	Design: pilot study Intervention: IDET vs. hypertonic dextrose/DMSO/glucosamine/chondroitin sulfate Sample size: 109 [34 prolo]	50% dextrose + 0.5% chondroitin sulfate + 20% glucosamine hydrochloride + 12% DMSO + 2% bupivacaine	Pain relief was statistically significant for both procedures, but slightly better for injections (2.2 VAS) than for IDET (1.27 VAS) (P = 0.01). Patients receiving injections were significantly more satisfied with the results of treatment. Only 47.8% of IDET patients reported that they felt better, whereas 65.6% of injection patients reported this outcome. Amongst IDET patients, 35.8% reported they were worse, while no	VAS, satisfaction rate, and flare-up before and after the procedures

Table 1. (Continued)

Author (Year)	Level of Evidence	Study Details	Composition	Results	Pain Outcome Measures
		Follow-up: IDET average 15.5 months and prolotherapy 7.7 months		restorative injection patient reported worsening of pain. Post-procedure flare-up occurred more frequently after restorative injection (81%) than after IDET (68.9%) and was more severe (7.9 vs. 6.1 VAS, respectively). Duration of pain flare-up was notably shorter for restorative injections (8.6 days) than for IDET (33.1 days).	
(c) MSC					
Noriega et al.[48] (2017)	I	Design: RCT Intervention: BMAC-MSC vs. sham paravertebral muscular injection Sample size: 24 [12 MSC] Follow-up: 12 months	Allogenic BMAC (25×10^6 MSC in 2 mL of saline per disc) Control: 2 mL of 1% mepivacaine	Significant improvement in VAS and ODI at 3 months that was sustained through 12 months. There was no significant improvement observed in the control group.	VAS, ODI, SF-12, MRI
Pettine et al.[49] (2017)	IV	Design: prospective, open-label, non-randomized, single-arm study Intervention: BMAC-MSC Sample size: 26 Follow-up: 3 years	2 to 3 mL of autologous BMAC (2,702/mL mesenchymal cell concentration)	77% of treatment group had significant improvement in VAS and ODI sustained through 36 months. MRI at 1 year demonstrated one modified Pfirrmann Grade improvement in 18/20 patients and no worsening on MRI.	VAS, ODI, MRI
Orozco et al.[50] (2011)	IV	Design: pilot phase I trial Intervention: autologous expanded BMAC-MSC Sample size: 10 Follow-up: 12 months	Autologous BMAC ($23 \pm 5 \times 10^6$ MSCs)	Significant improvement in VAS and ODI at 3 months that was sustained through 12 months. 85% of total improvement occurred in the first 3 months. Additionally, disc water content was significantly increased at 12 months, though there was no significant increase in disc height.	VAS, ODI, MRI
Coric et al.[54] (2013)	IV	Design: phase I, investigational, new drug, single-arm, prospective feasibility study Intervention: allogenic juvenile chondrocytes ×1 Sample size: 15 Follow-up: 12 months	Culture-expanded allogenic juvenile chondrocyte cells (10^7 cells/mL + fibrin carrier)	Mean ODI, NRS, and SF-36 overall significantly improved from baseline. Of the 9 patients with HIZ at baseline, 8 (89%) either showed improvement or resolution at 6 months (the 9th showed improvement at 3 months without further follow-up). 10 (77%) of 13 patients with follow-up MRI at 6 months demonstrated improvement, with 8 of 10 having sustained or continued improvement at 12 months.	ODI, NRS, SF-36, MRI
Mochida et al.[55] (2015)	IV	Design: prospective clinical study Intervention: NP chondrocytes + autologous BMAC-MSC in adjacent fusion level post-op day 7 Sample size: 9 Follow-up: 3 years	Autologous NP chondrocytes co-cultured with BMAC-MSCs (1×10^6 cells/702 μL sterile saline)	Viable NP cells from the fused disc were co-cultured in direct contact with autologous bone marrow–derived MSCs. One million activated NP cells were transplanted into the degenerated disc adjacent to the fused level at 7 days after the first fusion surgery. Significant improvement in JOA pain scores at 36 months compared to baseline. Injection occurred 7 days after fusion surgery.	JOA, MRI
Kumar et al.[53] (2017)	IV	Design: single-arm, open-label, phase I clinical trial Intervention: ADSCs + HA ×1 Sample size: 10 Follow-up: 12 months	Culture-expanded ADSCs + HA derivative (2×10^7 cells/disc [$n = 5$] or 4×10^7 cells/disc [$n = 5$])	Significant improvement in VAS, ODI, and SF-36 in both groups (low and high cell doses) without differences between groups. 6 (60%) of patients achieved treatment success with pain reduction of 50% or greater, and improved ODI and SF-36. 3 of these 6 additionally had improved disc water content.	VAS, ODI, SF-36, MRI, x-ray
Haufe[52] (2006)	IV	Design: prospective case series Intervention: BMAC-MSC ×1 Sample size: 10 Follow-up: 12 months	1 mL BMAC MSC + hyperbaric O_2 treatment (cell count not reported)	No significant improvement in back pain at 12 months.	Pain score

Table 1. (Continued)

Author (Year)	Level of Evidence	Study Details	Composition	Results	Pain Outcome Measures
Centeno et al.[51] (2017)	IV	Design: pilot study Intervention: 2 weeks pre-tx, 3 to 5 mL TFESI of autologous PL at affected disc level Treatment, BMAC-MSC + PL 10% to 20% 2 weeks post-tx, 3 to 5 mL TFESI of autologous PL at affected disc level Sample size: 33 Follow-up: 6 years	1 to 3 mL culture-expanded, autologous, BMAC MSCs + autologous PL 10% to 20% (cell count not reported)	NPS scores relative to baseline were significant at 3, 36, 48, 60, and 72 months post-treatment. The average modified SANE ratings showed a mean improvement of 60% at 3 years post-treatment. FRI post-treatment change score averages exceeded the minimal clinically important difference at all time points except 12 months. Twenty of the patients treated underwent post-treatment MRI and 85% had a reduction in disc bulge size, with an average reduction size of 23% post-treatment.	NPS, a modified SANE, FRI, measurement of the intervertebral disc posterior dimension, and adverse events

(a) A, activation (+ = yes; – = no); ASC, adipose signaling cells; BDI, Beck Depression Inventory; BMAC, bone marrow aspirate concentrate; FRI, functional rating index; GF, growth factors; L, leukocyte content (+ = >1%; – = <1%); MSC, mesenchymal signaling cells; NASS, North American Spine Society; NR, not reported; NRS, numeric rating scale; ODI, Oswestry Disability Index; P, platelet count; PPI, present pain intensity; PRGF, plasma rich in growth factor; PRP, platelet-rich plasma; R, red blood cell content (+ = >1%; – = <1%); RCT, randomized controlled trial; SF-12, 12-item Short Form Health Survey; SF-36, 36-item Short Form Health Survey; SVF, stromal vascular fraction; VPS, verbal pain scale.
(b) DMSO, dimethylsulfoxide; IDET, intradiscal electrothermal annuloplasty; NPS, numerical pain score.
(c) ADSCs, adipose-derived signaling cells; HA, hyaluronic acid; HIZ, high-intensity zone; JOA, Japanese Orthopaedic Association score; NP, nucleus pulposus; PL, platelet lysate; SANE, single-assessment numerical evaluation; TFESI, transforaminal epidural steroid injection.

Prolotherapy. Table 1b summarizes the characteristics and results of the currently available studies regarding intradiscal prolotherapy. There are 2 published studies on the use of prolotherapy for discogenic spine pain. Both studies reported positive results but are limited by being low level studies (III/IV). Additionally, the efficacy of intradiscal prolotherapy is difficult to ascertain in the case of Derby et al. because the injectate was a mixture of hypertonic dextrose, glucosamine/chondroitin, and dimethylsulfoxide. Having said that, this study demonstrated that intradiscal prolotherapy, in combination with the aforementioned substances, provided significant pain improvement compared to a intradiscal electrothermal treatment group.[46] In the other intradiscal prolotherapy study, a prospective series on 76 patients, slightly less than half had sustained improvement in numeric pain scores at 18 months.[47]

MSCs. Table 1c summarizes the characteristics and results of the currently available studies regarding intradiscal injection of MSCs. One level I study was available, where VAS, ODI, and lumbar disc degeneration assessed using the Pfirrman grading system significantly improved in a randomized controlled trial of intradiscal BMAC injection compared to sham (1% mepivacaine) injection.[48] The remaining literature consists of prospective or pilot studies. Four studies analyzed the effects of intradiscal injection of MSCs. Three showed improvement in measured pain and disability scores with follow-up periods of at least 1 year.[49–51] The lone negative study showed no improvement in numeric pain scores at 1 year after intradiscal injection of BMAC-MSCs followed by a 2-week course of hyperbaric oxygen therapy.[52]

Three additional studies were included in this review, yet they utilized different injectates, which needs to be taken into account when interpreting their results. Kumar et al.[53] used a combination of ASCs and hyaluronic acid derivatives for their injectate. This study found that 60% of participants achieved 50% or greater reduction of pain. Coric et al.[54] used allogenic juvenile chondrocyte cells for their injectate. The decision was made to include this study because the intervertebral disc is a fibro-cartilaginous structure, and the injectate used was a precursor to this. Mochida et al.[55] used a combination of nucleus pulposus chondrocytes co-cultured with BMAC-MSCs for their injectate. Each of these studies found significant improvement in pain scores after treatment.[54,55]

Facet Joint Orthobiologic Studies

Table 2 outlines the relevant facet joint orthobiologic studies culled from the literature.

PRP. Table 2a summarizes the characteristics and results of the currently available studies regarding facet joint PRP. One level I study was available that addressed treating facet joint–mediated pain with PRP. Wu et al.[56] found that intra-articular facet joint injections with PRP vs. corticosteroid/local anesthetic both resulted in significant improvement in VAS, RMQ, and ODI scores at 1 month, while only the PRP group had sustained improvement through 6 months. There were 3 additional level IV studies regarding the use of PRP for facet joint–mediated pain. Wu et al.[57] previously published a prospective series that found significant improvement in VAS scores at rest and with flexion, as well as improved RMQ and ODI scores at 3 months. Additionally, level IV studies via a retrospective observational study and case series both showed decreases in VAS scores.[44,58] It is noteworthy that the Kirchner et al.[44] study discussed earlier (see the section on PRP under Discogenic Orthobiologic Studies) is again included here. It is also worth noting that Aufiero et al.[58] injected both the intra-articular facet joints as well as surrounding ligaments. This should be considered when interpreting those results.

Prolotherapy. Table 2b summarizes the characteristics and results of the currently available studies regarding facet joint prolotherapy. One level I study exists that addresses the treatment of facet joint–mediated pain using prolotherapy. Dechow et al. found no significant difference in pain outcomes (short-form McGill Pain Questionnaire) at 6 months between the treatment group and the normal saline with 1% lignocaine control group. Notably, the injectate used for this study was a mixture of hypertonic dextrose, glycerine, phenol, and lignocaine. Additionally, not only were the facet joints injected, but so were several locations along the iliolumbar and posterior sacroiliac (SI) ligaments. The results of this study should be interpreted with these caveats in mind.[59] Additionally, there were 3 published studies by Hooper and colleagues, with 1 being prospective and 2 retrospective. The prospective study found that intra-articular facet joint prolotherapy with 20% dextrose provided significant improvement on multiple analyzed disability scales over a 12-month period.[60] The vast majority of patients reported a reduction in their level of pain, improvement in activities of daily living, and ability to work in a retrospective case series on 177 patients with chronic spinal pain treated with 20% dextrose prolotherapy facet joint injections.[61] The final study had a much lower sample size of 15 patients with chronic cervical whiplash, and demonstrated a significant reduction in neck disability index scores.[62] All 3 studies by Hooper and colleagues involved facet joint intervention in the cervical spine for at least a portion of their cohort.

MSCs. No studies to date have been published on the use of MSCs administered to the facet joints.

Epidural Orthobiologic Studies

Table 3 outlines the relevant epidural orthobiologic studies culled from the literature.

PRP. Table 3a summarizes the characteristics and results of the currently available studies regarding epidural injection of PRP. The only level I epidural study does not actually involve PRP, but an analog called autologous conditioned serum (ACS), which is similarly obtained through phlebotomy but instead functions as an anti-inflammatory agent through interleukin antagonism promotion. Pain reduction in both the ACS and steroid control groups was observed, with more sustained pain relief in the ACS group.[63] Two other prospective studies currently exist, with a registry of 470 patients treated with platelet lysate (PL) by Centeno et al.[64] being the largest and observing significant numeric pain score changes through all time points compared to baseline. While there were no serious adverse events reported, 6.3% reported mild adverse events related to the treatment. PL is slightly different from PRP in that PL is created by lysing platelets and removing the cell debris. This resultant product is rich in growth factors (similar to PRP) but devoid of other platelet material. This should be taken into account when interpreting results. Correa et al.[65] found that epidural autologous leukocyte-reduced PRP significantly improved VAS scores and Macnab criteria findings for 250 patients throughout 2 years of follow-up in the other prospective study.

Retrospective analyses comprise the remaining 3 publications. Two showed VAS score improvement after epidural PRP administration that was sustained for 3 months in one and 6 months in the other.[44,66] It is noteworthy that the Kirchner et al.[44] study discussed

Table 2. Facet Joint Orthobiologic Studies—(a) PRP; (b) Prolotherapy

Author (Year)	Level of Evidence	Study Details	Composition	Results	Pain Outcome Measures
(a) PRP					
Wu et al.[56] (2017)	I	Design: prospective randomized controlled study Intervention: PRP vs. LA/CS Sample size: 46 (23 PRP) Follow-up: 6 months	P: 0.5 mL 100 to 300 × 10^9/mL L: NR R: – A: NR Control: 0.5 mL of 0.5% lidocaine and 5 mg/mL betamethasone (4:1)	Significant improvement in VAS, RMQ, and ODI in both groups at 1 month; only the PRP group sustained improvement at 6 months.	VAS ODI RMQ
Wu et al.[57] (2016)	IV	Design: prospective series Intervention: autologous PRP Sample size: 19 Follow-up: 3 months	P: 0.5 mL 100 to 300 × 10^9/mL L: NR R: NR A: NR	Significant improvement in VAS at rest and with flexion, RMQ, and ODI at 3 months. 79% with outcomes assessed as "excellent" at 3 months.	VAS ODI RMQ
Kirchner and Anitua[44] (2016)	IV	Design: observational retrospective pilot study Intervention: 1 intradiscal, 1 intra-articular facet, and 1 transforaminal epidural injection of PRGF-Endoret Sample size: 86 Follow-up: 6 months	P: 4 mL (2× peripheral blood) L: NR R: NR A: + PRGF activator ($CaCl_2$)	After PRGF injection to intervertebral disc, transforaminal epidural injection, and facet joints, significant improvements in VAS scores were obtained with 91% of patients showing an excellent score, 8.1% with moderate improvement, and 1.2% with lack of response.	VAS
Aufiero et al.[58] (2015)	IV	Design: case series Intervention: series of 3 PRP facet + ligament injections Sample size: 5 Follow-up: 6 to 12 months	P: > 1.5 × 10^6 L: – R: – A: –	All reported symptom relief and decrease in VAS at follow-up. Case 1: 100% improvement and return to sport at 6 months. Case 2: 1/10 VAS score at 9 months. Case 3: 2/10 VAS score and improvement in functional status at 12 months. Case 4: 70% symptom improvement and increased functional status after series of 3. Case 5: 65% to 70% symptom improvement and increased functional status at 6-month follow-up.	VAS
(b) Prolotherapy					
Dechow et al.[59] (1999)	I	Design: randomized, double-blind, placebo-controlled trial Intervention: lumbar prolotherapy + (3 injections) + iliolumbar/SI ligaments Sample size: 74 Follow-up: 6 months	Treatment: 5 mL 25% dextrose/25% glycerine/2.4% phenol + 5 mL 1% lignocaine Control: 5 mL NS + 5 mL 1% lignocaine	No statistically significant difference in pain outcomes at 6 months in treatment vs. control group. Both groups demonstrated a downward trend but did not reach statistical significance	SF-MPQ
Hooper et al.[60] (2011)	III	Design: prospective case series Intervention: C/T/L Prolotherapy ± iliolumbar/SI ligaments (3 to 6 injections) Sample size: 147 Follow-up: 12 months	0.5 mL 20% dextrose + 0.75% lidocaine	Both litigants (71) and non-litigants (76) showed significant improvement from baseline on all disability scales ($P < 0.001$). There were no differences in the percentage of litigants/non-litigants reporting improvement on impression of change scales for symptoms (91/92%), function (90/90%), improved ability to work (76/75%), willingness to repeat	NDI, Patient Specific Functional Scale, and RMQ

Table 2. (Continued)

Author (Year)	Level of Evidence	Study Details	Composition	Results	Pain Outcome Measures
				treatment (91/93%), ability to decrease medication (82/81%), and decreased need for other treatment (80/84%).	
Hooper and Ding[61] (2004)	IV	Design: retrospective case series Intervention: *C/T/L* Prolotherapy ± iliolumbar/SI ligaments (3 to 6 injections) Sample size: 177 Follow-up: 2 months to 2.5 years	0.5 mL 20% dextrose + 0.75% lidocaine	91% of patients reported reduction in level of pain, 85% of patients reported improvement in activities of daily living, and 84% reported an improvement in ability to work.	NPS
Hooper[62] (2007)	IV	Design: case series Intervention: B/I 3 level C-spine prolotherapy Sample size: 15 Follow-up: 12 months	0.5 to 1 mL 20% dextrose + 1% lidocaine	Mean NDI pre-treatment was 24.71 and decreased post-treatment to 14.21 (2 months), 13.45 (6 months), and 10.94 (12 months). Average change NDI = 13.77 ($P < 0.0001$) baseline vs. 12 months.	NDI

(a) A, activation (+ = yes; – = no); CS, corticosteroid; L, leukocyte content (+ = >1%; – = <1%); LA, local anesthetic; NR, not reported; ODI, Oswestry Disability Index; P, platelet count; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; R, red blood cell content (+ = >1%; – = <1%); RMQ, Roland-Morris Disability Questionnaire.
(b) *C/T/L*, cervical/thoracic/lumbar; NDI, Neck Disability Index; NPS, numerical pain scale; NS, normal saline; SF-MPQ, short-form McGill Pain Questionnaire; SI, sacroiliac.

earlier (see PRP section under Discogenic Orthobiologic Studies) is again included here. The study by Bhatia et al.[66] also found that all participants were able to maintain daily activities without the use of pain medications. Additionally, Ravi Kumar showed that VAS scores were improved in 20 patients treated with epidural ACS.[67]

Prolotherapy. Table 3b summarizes the characteristics and results of the currently available studies regarding epidural prolotherapy. There was one level I study, which demonstrated epidural prolotherapy to be efficacious in relieving pain for up to 48 hours, but the results did not differ from placebo at 2 weeks.[68] That same group assessed repeat injections as needed over the course of 1 year in the previous study cohort and found clinically significant improvement in NRS and ODI outcome measures.[69] These studies highlighted the issues with single-injection prolotherapy and the need to assess the effect of serial prolotherapy epidural injections for long-term pain relief.

MSCs. No studies to date have been published on the use of MSCs administered via epidural placement.

Sacroiliac Joint Orthobiologic Studies

Table 4 outlines the relevant sacroiliac joint orthobiologic studies culled from the literature.

PRP. Table 4a summarizes the characteristics and results of the currently available studies regarding SIJ injection of PRP. There was one level I study, which demonstrated significant improvement from baseline after both SIJ injection of PRP as well as steroid injection with triamcinolone at 3 months. Patients in the PRP group maintained 90% efficacy at 3 months, while the steroid group maintained 25% efficacy. Modified ODI and SF-12 scores gradually improved in the PRP group through 3 months, while the steroid group demonstrated initial improvement at 4 weeks with subsequent deterioration at 3 months.[70] Additionally, there were two level IV studies that demonstrated significant pain reduction at 1 year, with one study demonstrating sustained clinical benefits through 4 years.[71,72] Noteworthy, Ko et al. injected PRP at Hackett points A, B, and C (posterior SI ligaments). Although their target was not truly intra-articular SIJs, the decision was made to include this study within the review because of the

Table 3. Epidural Orthobiologic Studies—(a) PRP; (b) Prolotherapy

Author (Year)	Level of Evidence	Study Details	Composition	Results	Pain Outcome Measures
(a) PRP					
Becker et al.[63] (2007)	I	Design: P-DB-Ref CT Intervention: ACS vs. 5 mg or 10 mg triamcinolone Sample size: 84 Follow-up: 6 months	IL-1 RA-enriched ACS Control: 5 mg or 10 mg of triamcinolone	All 3 groups had clinically remarkable and statistically significant reductions in VAS and ODI. ACS with consistent pattern of superiority to triamcinolone from week 12 to final evaluation at week 22 in VAS. No statistically significant difference between the 2 triamcinolone dosages during the study period.	VAS ODI
Correa et al.[65] (2019)	IV	Design: prospective observational, non-randomized Intervention: C/L spine PRGF ×2 Sample size: 250 Follow-up: 2 years	PRGF P: 10 to 12 mL L: NR R: NR A: NR	Significant improvement in VAS scores and Macnab criteria findings through 2 years of follow-up.	VAS Modified Macnab criteria
Centeno et al.[64] (2017)	IV	Design: prospective registry Intervention: PL Sample size: 470 Follow-up: 2 years	3 to 5 mL PL 50%, 4% lidocaine 25%, and compounded preservative-free 100 to 200 ng/mL hydrocortisone 25%	Post PL treatment, significantly lower ($P < 0.0001$) NPS and FRI change scores at all time points compared to baseline. Post-treatment FRI change score means exceeded the minimal clinically important difference beyond 1 month. Average modified SANE ratings showed 49.7% improvement at 24 months post-treatment. Twenty-nine patients (6.3%) reported mild adverse events related to treatment.	NPS FRI SANE
Ravi Kumar et al.[67] (2015)	IV	Design: case series Intervention: ACS (1 to 3 injections) Sample size: 20 Follow-up: 6 months	2 mL IL-1 RA-enriched ACS	Statistically significant changes in quadruple VAS, rODI, SF-12 from pre-injection to first, second, and third follow-ups ($P < 0.001$).	VAS
Kirchner and Anitua[44] (2016)	IV	Design: observational retrospective pilot study Intervention: 1 intradiscal, 1 intra-articular facet, and 1 transforaminal epidural injection of PRGF-Endoret Sample size: 86 Follow-up: 6 months	P: 4 mL (2× peripheral blood) L: NR R: NR A: + PRGF activator ($CaCl_2$)	After PRGF injection to intervertebral disc, transforaminal epidural injection, and facet joints, significant improvements in VAS scores were obtained, with 91% of patients showing an excellent score, 8.1% with moderate improvement, and 1.2% with lack of response.	VAS
Bhatia and Chopra[66] (2016)	IV	Design: case series Intervention: PRP ×1 Sample size: 10 Follow-up: 3 months	P: 5 mL L: NR R: NR A: NR	All showed improvements in VAS, SLRT, and mODI index, which were sustained at 3 months. 90% had VAS ≤ 4 at 3 months.	VAS
(b) Prolotherapy					
Maniquis-Smigel et al.[68] (2016)	I	Design: RCT Intervention: caudal prolotherapy vs. NS control ×1 Sample size: 35 (19 prolotherapy) Follow-up: 2 weeks	10 mL 5% dextrose Control: 10 mL 0.9% NS	Significant difference in NRS pain score up to 48 hours but not at 2 weeks. 84% (16/19) of dextrose recipients and 19% (3/16) of saline recipients reported ≥50% pain reduction at 4 hours.	NRS
Maniquis-Smigel et al.[69] (2018)	IV	Design: prospective uncontrolled Intervention: caudal prolotherapy (5.5 ± 2.9 injections) Sample size: 32 Follow-up: 1 year	10 mL 5% dextrose	Compared with baseline status, NRS and ODI scores improved by 3.4 ± 2.3 points (52%) and 18.2 ± 16.4 points (42%), respectively ($P < 0.001$) at 1 year. The fraction of participants with 50% reduction in NRS-based pain was 21/32 (66%).	NRS

(a) A, activation (+ = yes; − = no); ACS, autologous conditioned serum; C/L, cervical/lumbar; FRI, functional rating index; IL-1, interleukin-1; L, leukocyte content (+ = >1%; − = <1%); mODI, modified Oswestry Disability Index; NPS, numerical pain scale; NR, not reported; ODI, Oswestry Disability Index; P-DB-Ref CT, prospective double blinded reference controlled trial; P, platelet count; PL, platelet lysate; PRGF, plasma rich in growth factors; PRP, platelet-rich plasma; R, red blood cell content (+ = >1%; − = <1%); RA, receptor antagonist; rODI, revised Oswestry Disability Index; SANE, Single Assessment Numerical Evaluation; SF-12, 12-item Short Form Health Survey; SLRT, straight leg raising test.
(b) NRS, numeric rating scale; NS, normal saline; RCT, randomized controlled trial.

Table 4. Sacroiliac Joint Orthobiologic Studies—(a) PRP; (b) Prolotherapy

Author (Year)	Level of Evidence	Study Details	Composition	Results	Pain Outcome Measures
PRP					
Singla et al.[70] (2017)	I	Design: PROBE study Intervention: PRP vs. steroid Sample size: 40 Follow-up: 3 months	Group P: P: 3 mL L: – R: NR A: 0.5 mL $CaCl_2$ Group S: 3 mL methylprednisolone (40 mg/mL) with 2% lidocaine and saline	Pain significantly less at 6 weeks and 3 months in group P vs. S. The efficacy of steroid injection was reduced to only 25% at 3 months in group S, while it was 90% in group P. A strong association was observed in patients receiving PRP and showing a reduction of VAS ≥ 50% from baseline when other factors were controlled. The mODI and SF-12 scores were improved initially for up to 4 weeks but deteriorated further at 3 months in group S, while both the scores improved gradually for up to 3 months in group P.	VAS, mODI, SF-12
Ko et al.[71] (2017)	IV	Design: case series Intervention: Hackett points A, B, and C injections ×2 Sample size: 4 Follow-up: 4 years	P: 10 mL (5 to 6× > baseline) L: NR R: NR A: NR 0.5 mL with each needle contact of the ligament-bone interface at Hackett points A, B, and C	Clinically and statistically significant reduction in pain at 1 year post-treatment, as evidenced by a 93%, 88%, and 75% reduction in the mean SFMPQ ($P < 0.0001$), NRS ($P < 0.001$), and ODI ($P < 0.0001$) scores, respectively. The clinical benefits of PRP were still significant at 4 years post-treatment. Additionally, patients achieved an improvement in their quality of life and returned to their pre-injury statuses	SFMPQ, NRS, ODI
Navani and Gupta[72] (2015)	IV	Design: case series Intervention: PRP ×1 Sample size: 10 Follow-up: 12 months	P: 4 mL L: NR R: NR A: NR	VAS scores for all patients decreased more than 50% and their function increased for the period of 12 months.	VAS, SF-36
(b) Prolotherapy					
Kim et al.[73] (2010)	I	Design: RCT Intervention: bi-weekly prolotherapy vs. steroid, max 3 injections. Sample size: 48 (23 prolotherapy) Follow-up: 15 months	2.5 mL 25% dextrose	Both groups' NRS and ODI scores significantly improved from baseline at 2 weeks; no significant difference between the two. Cumulative incidence of ≥ 50% pain relief at 15 months was 58.7% for prolotherapy group vs. 10.2% in steroid group. Statistically significant difference between the two at 15 months.	NRS ODI
Hoffman and Agnish[74] (2018)	III	Design: retrospective cohort study Intervention: prolotherapy ×3 (1 month intervals) Sample size: 103 Follow-up: ~4 months	15% dextrose (3 mL 50% dextrose + 7 mL 1% lidocaine)	24 (23%) achieved ODI improvement of ≥15 points (ie achieved MCID), 29 (28%) had ODI improvement of <15 points, and 50 (49%) had unchanged or worsened ODI scores. 15-point improvement in ODI scores prior to the second prolotherapy injection had a sensitivity of 92% and specificity of 80% for determining which patients would improve.	ODI

(a) A, activation (+ = yes; – = no); L, leukocyte content (+ = >1%; – = <1%); mODI, modified Oswestry Disability Index; NR, not reported; NRS, numeric rating scale; ODI, Oswestry Disability Index; P, platelet count; PROBE, prospective, randomized, open, blinded end point; PRP, platelet-rich plasma; R, red blood cell content (+ = >1%; – = <1%); SF-12, 12-item Short Form Health Survey; SF-36, 36-item Short Form Health Survery; SFMPQ, short form McGill Pain Questionnaire.
(b) MCID, minimal clinically important difference; RCT, randomized controlled trial.

proximity of the posterior SI ligaments to the actual SIJ and the likelihood, given the high number of injections utilized, that some PRP was actually injected within the SIJ. This should be taken into account when interpreting their results.[71]

Prolotherapy. Table 4b summarizes the characteristics and results of the currently available studies regarding SIJ prolotherapy. There was one level I study, which compared SIJ injections with prolotherapy vs. steroid and found a significant difference with regard to achieving greater than or equal to 50% pain relief at 15 months post-procedure, 58.7% for the prolotherapy group and 10.2% for the steroid group.[73] Additionally, there was one level III study, which found that 23% of patients achieved a minimal clinically important difference in ODI score at 4 months following 3 SIJ prolotherapy injections.[74]

MSCs. No studies to date have been published on the use of MSCs administered via the SIJ.

CONCLUSIONS AND FUTURE RESEARCH RECOMMENDATIONS

We aimed to provide the reader with a clinical perspective on the existing orthobiologic literature for spine-related pain. At the time of this publication, there was one level I study that demonstrated positive results for each of the following: PRP and MSC injections for discogenic pain; facet joint injection of PRP; epidural injection of autologous conditioned serum; and PRP injection and prolotherapy for SIJ pain. Notably, no intervention has multiple published level I studies. In order to verify these findings, it is paramount that additional level I studies be conducted to replicate these positive results. The one level I study on facet joint prolotherapy found no significant benefit. It is important to remember that nonstandard injectate was used for this study. The one level I study on epidural prolotherapy found a significant difference in pain scores at 48 hours compared to the control group, but no significant difference at the 2-week endpoint. Thus far, the studies for intradiscal prolotherapy and epidural injection of PRP are limited to no higher than level III. MSCs have yet to be analyzed for any pain generator aside from the intervertebral disc.

Additional studies on spine-related pain are now being published at increasing rates as the science behind and evidence for regenerative medicine continues to expand for other musculoskeletal ailments.[12] Of the 35 reviewed articles, 25 have been published in the past 5 years. However, to support continued use, limitations in the current literature must be acknowledged and accounted for in future studies. As with all emerging therapies, a paucity of high-quality evidence hinders widespread acceptance. Additional level I/II/III studies should be prioritized. The vast majority of current studies have no comparative group. A starting point going forward would be to compare cohorts of patients treated with regenerative medicine to those treated with "standard of care."

Amongst all regenerative therapeutics evaluated, preparation consistency and reporting were severely lacking. Standardization of preparation reporting is a viable first step. Classification systems such as PLRA for PRP are a shining example, and additional systems for MSCs are needed. This will allow for better protocol reproducibility and improved comparison of treatment efficacy, which is currently precluded given the wide variability in existing literature.

In light of this large heterogeneity amongst orthobiologic preparations, injectate delivery method, location, and number of treatments, as well as the paucity of well-designed randomized controlled trials, the authors opted to present the current literature in the form of a narrative review. A few systematic reviews do exist in the literature on this topic.[75–78] Having said that, in the absence of improved standardization regarding the aforementioned points, the authors felt a narrative review that included the 3 most common orthobiologic agents used in the treatment of axial/radicular spine pain and the similarities/differences amongst the currently available studies would be most suitable for assistance when interpreting the current literature.

As the current landscape of medicine continues to evolve and regenerative interventions increasingly become a part of the dialogue between patients and providers, it is paramount that we continually review the most up-to-date evidence regarding the therapies and interventions we have to offer. This evidence-based approach to interventional selection provides the patient with the greatest likelihood of success, and demonstrates a responsibility of resources on the part of the provider. Our hope would be that this approach will help to maintain the durability of long-term access to these orthobiologic therapies and make them more accessible through insurance authorization.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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