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Regenerative Medicine Guidelines

Comprehensive Evidence-Based Guidelines for Regenerative Therapies in the Management of Chronic Low Back Pain: 2025 Update from the American Society Of Interventional Pain Physicians (ASIPP)

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Background: Regenerative medicine is an evolving medical subspecialty dedicated to enhancing the body's natural healing mechanisms to repair or replace damaged tissues. By using autologous or allogeneic biologics, it offers the potential to restore function where conventional therapies have shown limited success. While this field holds great promise and continues to generate enthusiasm among both patients and clinicians, it remains in early stages of clinical validation. Therefore, it must be approached with careful optimism and responsible application, ensuring that its presentation, promotion, and use in clinical settings are grounded in evidence and ethical standards.

Objective: To provide updated, evidence-based recommendations for the role of regenerative therapies in managing moderate to severe chronic low back pain.

Methods: A multidisciplinary panel of experts, convened by the American Society of Interventional Pain Physicians (ASIPP), systematically reviewed the current evidence and incorporated patient perspectives to develop practical, evidence-informed recommendations. The process included defining key clinical questions, reviewing the literature, formulating evidence-based statements, and reaching consensus through structured discussions and formal voting.

Results: A total of 35 authors contributed to the development of these guidelines, with 33 experts participating in the formal consensus process. Altogether, 19 recommendations were generated, with all of them achieving 100% agreement. These recommendations were informed by a comprehensive review of systematic reviews, randomized controlled trials (RCTs), and observational studies encompassing a broad range of regenerative therapies.

Evidence was appraised using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology to determine certainty levels. Both qualitative and quantitative analyses were applied to synthesize the best available data, resulting in evidence-based recommendations summarized below.

- Intradiscal Injections (PRP):
  Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate
- Intradiscal Injections (BMAC):
  Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate
- Epidural Injections (PRP):

Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate
- Facet Joint Injections (PRP and MSCs):
  Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Moderate
- Sacroiliac Joint Injections (PRP):
  Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Low
- Functional Spine Unit Injections
  Evidence Level: Very Low; Consensus-Based Clinical Recommendation: Low

Limitations: The primary limitation of these guidelines is the scarcity of high-quality studies, with much of the available evidence derived from small or heterogeneous trials.

Precautions: Regenerative therapies should be considered only after a thorough diagnostic evaluation confirming clinical necessity. Treatment decisions must account for the patient's medical condition, preferences, and expectations. Patients should be fully informed about the nature, potential benefits, risks, and costs of regenerative treatments, most of which are not covered by commercial insurance.

These therapies may be used alone or in conjunction with other evidence-based modalities, such as structured exercise, physical therapy, behavioral therapy, or conventional medical management. Clinicians must follow all applicable U.S. Food and Drug Administration (FDA) regulations and adhere to safety and ethical standards outlined in these guidelines.

Conclusion: Based on current evidence, lumbar intradiscal injections of platelet-rich plasma (PRP) and mesenchymal stem cells (MSCs) are supported by Level III evidence. Lumbar epidural PRP injections are also supported by Level III evidence, while PRP injections for lumbar facet joints and sacroiliac joints are supported by Level IV evidence. Given the emerging status of biologic therapies and the limited quality of existing studies, the panel provides moderate, consensus-based recommendations for the use of all biologics in the lumbar spine.

Key words: Chronic low back pain, discogenic pain, facet joint pain, sacroiliac joint pain, regenerative medicine, platelet-rich plasma, mesenchymal stem cells, stromal vascular fraction, exosomes, bone marrow concentrate, intradiscal injections, facet joint injections, sacroiliac joint injections, epidural injections, Food and Drug Administration, minimal manipulation

Disclaimer: These guidelines do not constitute inflexible treatment recommendations. Clinicians are expected to establish a plan of care on a case-by-case basis, considering an individual patient's medical condition, personal needs, and preferences, and the physician's experience. Consequently, these guidelines do not represent a "standard of care."

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SUMMARY OF RECOMMENDATIONS:

1. What are the available regenerative medicine therapies in the United States?

   Answer: Available regenerative medicine therapies include PRP and BMC when obtained with FDA-cleared devices.

   Evidence Level: High; Consensus-Based Clinical Recommendation: High

2. What are the potential regenerative medicine modalities are available in other countries but not the United States?

   Answer: Multiple therapies are not currently available due to FDA regulations in the United States. In other countries, multiple therapies are available, including adipose stem cells including stromal vascular fraction (SVF), autologous, allogenic, or stored stem cells, stem cells derived from umbilical cord and exosomes. There is no clear guidance on micronized fat and it is used by some in the field.

   Evidence Level: High; Consensus-Based Clinical Recommendation: High

3. What are the recognized risks of unapproved stem cell treatments.

   Answer: There are rare, but significant potential risks associated with unapproved stem cell treatments, including blindness, infections (like human immunodeficiency virus, hepatitis, or bacterial infections), thrombosis, tumor formation, neurological complications, and even death.

   Evidence Level: Moderate; Consensus-Based Clinical Recommendation: High

4. Defining Functional Spine Unit.

   Answer: A functional spinal unit (FSU), also known as spinal motion segment, or articular tide, is the smallest physiological unit of the spine that exhibits the same biomechanical properties of the entire spine. Each FSU is a 3-joint complex and is responsible for coordinated movement protecting neural structures and providing a stable base for the body. A FSU consists of 2 adjacent vertebrae, intervertebral disc, facet joints, ligaments, and muscles. The concept of FSU is crucial for understanding spine health and dysfunction related to degeneration, injury, diagnosis and treatment.

   Functional spine unit is utilized in managing back pain in regenerative medicine, in application of therapies in contrast to precision diagnosis and therapy with the single structure, as advocated in interventional pain management.

   While this approach appears to be appropriate considering that regenerative medicine therapies are not bound by LCDs and medical policies, functional spine unit may provide better results; however, there is no significant evidence at the present time.

   Evidence Level: Very Low; Consensus-Based Clinical Recommendation: Low

5. What are the identified risks of regenerative medicine therapies?

   Answer: Regenerative medicine therapies are similar to interventional techniques with low risk; however, severe complications can occur including infection, specifically, discitis, epidural hematoma, and abscess, superficial infections, allergies, neurological complications, tumor formation and death.

   Overall risk of interventional procedures has been considered by some as higher because of the steroid-based injections with chondrotoxicity, tenotoxicity, neurotoxicity, and multiple systematic toxicities. These toxicities are absent with PRP and BMC.

   Evidence Level: High; Consensus-Based Clinical Recommendation: High

6. Platelet Rich Plasma (PRP): Quality and Standards

   Answer: Key issues concerning quality and standards for platelet-rich plasma include a lack of standardized protocols, variations in preparation techniques, and regulatory limitations.

   Unlike pharmaceuticals, no universally accepted standard defines the optimal concentration of cells and growth factors. Different conditions may benefit from different formulations (leukocyte-rich versus leukocyte-poor).

   Quality assurance practices include process validation, testing and monitoring, traceability, and device selection.

   Evidence Level: Low; Consensus-Based Clinical Recommendation: Moderate

7. Bone Marrow Aspirate Concentrate (BMAC): Quality and Standards

   BMAC devices are expected to produce viable cells with cell viability rates of approximately 90%. The quality of BMAC is heavily dependent on the aspiration technique. Volume and site are important.

   There are no established standardized protocols. Consequently, there are variations in preparation technique limited by regulatory standards. Minimum requirements for BMAC include qualifying mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs).

   Different processing devices and methods produce different results.

   Quality assurance practices include process validation, testing and monitoring, traceability, and device selection

   Evidence Level: Low; Strength of Recommendation: Moderate

8. Minimum required quality control measures:

   Answer: The minimum required quality control measures for clinical purposes include final volume, platelet count, white blood cell (WBC) count, red blood cell (RBC) count, and the concentration factor relative to whole blood. Further, different processing devices and methods produce different results regarding final cell counts, viability, and volume.

   Evidence Level: Moderate; Consensus-Based Clinical Recommendation: Moderate

9. Minimum required platelets per injection:

   Answer: Studies show that a minimum of 4 billion and 10 billion as optimum count of platelets per injection is needed for a significant clinical effect in knee intraarticular injections. Even though limited, literature is available regarding spinal injections, based on other joints, a cumulative dose of around 10 billion platelets into structures of a FSU are recommended. There is literature showing intradiscal injections of PRP with greater than 10 times baseline platelet concentrations resulted in greater improvements in pain scores and functional outcomes at long-term follow-up compared to lower concentration PRP less than five times.

   Evidence Level: Low; Consensus-Based Clinical Recommendation: Moderate

10. It is essential to understand PRP and BMAC with multiple variations and the effectiveness, technical considerations, and complications with the spinal injections.

    Evidence Level: High; Consensus-Based Clinical Recommendation: High

11. Based on the available evidence and all available guidance, patient education is a crucial aspect of the success of regenerative medicine injections.

    Evidence Level: High; Consensus-Based Clinical Recommendation: High

12. What is the evidence of effectiveness for PRP and consensus-based clinical recommendations for intradiscal therapy.

    Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate

13. The evidence of effectiveness for BMAC and consensus-based clinical recommendations for intradiscal therapy.

    Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate.

14. The evidence of effectiveness and consensus-based clinical recommendations for epidural injections with PRP in managing low back and lower extremity pain due to degenerative disc pathology and other conditions.

    Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate

15. The evidence of effectiveness and consensus-based clinical recommendations for facet joint intraarticular PRP and MSC injections in managing chronic low back pain.

    Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Moderate

16. The evidence of effectiveness and consensus-based clinical recommendations for sacroiliac joint PRP injections.

    Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Low

17. The guidelines for administration of biologics include failure of conservative modalities, understanding of the risks and benefits, willingness to participate in rehabilitation program and appropriate consent with shared decision making.

    Evidence Level: High; Consensus-Based Clinical Recommendation: High

18. Risk stratification for regenerative medicine therapies, based on ASIPP guidelines: high risk for intradiscal therapy, moderate risk for epidural injections, low risk for facet joint injections, and low risk for sacroiliac joint injections.

    Evidence Level: Moderate; Consensus-Based Clinical Recommendation: Moderate

19. Antiplatelet and anticoagulant therapy guidelines in continuation, discontinuation, and re-establishment are utilized per ASIPP guidelines for low- and high-risk procedures.

    Evidence Level: Moderate; Consensus-Based Clinical Recommendation: Moderate

Index - Regenerative Therapies in the Management of Chronic Low Back Pain Guidelines 2025

1.0 Introduction

Regenerative medicine is the science dedicated to the repair, restoration, and regeneration of diseased or injured cells, tissues, or organs to reestablish homeostasis and improve functionality. This multidisciplinary specialty encompasses advanced research that translates from laboratory discovery to clinical applications, spanning from tissue engineering to cellular biology. These efforts have produced a range of injectables, implants, and scaffolds designed to replicate normal tissue structure and function (1-28). Regenerative medicine represents a transformative approach to health care by activating the body's natural repair mechanisms to restore function in tissues and organs previously considered irreparable (23).

Cell biology focuses on the structure, function, and behavior of cells as the fundamental units of all organisms, while tissue engineering combines cells, engineering methods, materials, and biochemical and physicochemical factors to improve or replace biological tissues. Although the term regenerative medicine is sometimes used interchangeably with tissue engineering, the broader field of regenerative medicine incorporates multiple techniques, including prolotherapy, platelet-rich plasma (PRP), and stem cell therapy.

In contemporary practice, the 2 primary components of regenerative medicine in chronic pain management are PRP and stem cell therapy, with exosomes representing an emerging area of application. Many clinicians consider PRP or stem cell injections as effective treatments for degenerative spinal and musculoskeletal conditions (1-22). While these approaches remain under active investigation and debate, enthusiasm for evidence-based regenerative interventions continues to grow. Nonetheless, optimism is tempered by skepticism and concern regarding potential misuse, overuse, and regulatory challenges, which remain frequent topics of professional and public discourse (1-4,12-16,29-37).

The literature often describes the "good," "bad," and "ugly" aspects of regenerative medicine (16). The "good" lies in its potential to repair or replace damaged tissues and organs, offering new hope for previously untreatable conditions. The "bad" involves uncertain long-term outcomes, limited high-quality clinical data, and the significant cost associated with many therapies. The "ugly" encompasses unethical practices, including exploitation of vulnerable patients through unproven stem cell interventions and the risks of tumorigenicity linked to some regenerative products. PRP applications for many conditions are relatively noncontroversial apart from cost considerations, whereas bone marrow concentrate (BMC) injections, though promising, present greater technical difficulty and expense. Most of the controversy and regulatory scrutiny, however, surrounds stem cell therapies (16).

The U.S. Food and Drug Administration (FDA) continues to issue guidance and warnings regarding the use of stem cells. As of July 2025, enforcement actions remain active against products derived from stromal vascular fraction (SVF), umbilical cord blood, and exosomes. Courts have upheld the FDA's authority to regulate these products as drugs and/or biologics, requiring them to meet established safety and efficacy standards. In parallel, the Federal Trade Commission (FTC) has pursued legal action against clinics engaged in deceptive advertising or marketing of unproven cell-based therapies. The FDA has also increased oversight of clinical trials, halting new studies that involve exporting patients' cells to foreign laboratories for genetic modification and reinfusion, citing concerns about data security and informed consent.

The FDA specifically warns against stem cell tourism due to serious risks associated with unapproved treatments, including blindness, infections such as human immunodeficiency virus or hepatitis, tumor formation, neurological complications, and even death. Approved regenerative treatments remain extremely limited; only a few stem cell products are authorized for specific indications such as certain cancers, blood disorders, and immune deficiencies. Accordingly, stem cell products derived from SVF, umbilical cord blood, and exosomes are not approved for clinical use in treating musculoskeletal conditions.

Although the utilization of regenerative therapies has expanded widely, accurate data on their prevalence and outcomes remain scarce. While numerous guidelines exist for managing spinal pain, including interventional pain management and surgical procedures (38-45), few provide high-quality, evidence-based recommendations specific to regenerative medicine in musculoskeletal disorders (2,4).

The American Society of Interventional Pain Physicians (ASIPP) has been instrumental in developing evidence-based guidelines for interventional pain techniques, opioid management, peripheral nerve stimulation, perioperative anticoagulant and antiplatelet therapy, and regenerative interventions (2,39-42,44,45). This current update continues ASIPP's commitment to advancing safe and effective biologic applications for low back pain management. These

guidelines summarize the available literature on PRP and bone marrow aspirate concentrate (BMAC) injections targeting the lumbar spine, including intervertebral discs, facet joints, sacroiliac joints, paraspinal muscles, ligaments, and tendons, and incorporate relevant national and international regulatory and bioethical considerations. They also outline the clinical protocols and procedural standards required to deliver these therapies responsibly in a safe, compliant, and professional environment.

2.0 Methods

2.1 Rationale

Interventional pain management is defined as "the discipline of medicine devoted to the diagnosis and treatment of pain-related disorders, principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain, independently or in conjunction with other modalities of treatment" (46). Interventional pain management techniques are defined as "minimally invasive procedures including percutaneous precision needle placement, with placement of pharmaceuticals in targeted areas or ablation of targeted nerves; and some surgical techniques such as laser or endoscopic diskectomy, placement of intrathecal infusion pumps, and spinal cord stimulators, for the diagnosis and management of chronic, persistent, or intractable pain" (47).

Recent literature has shown a pattern of significant growth, followed by deceleration and eventual decline in the use of several interventional procedures, with the exception of spinal cord stimulation (48-54). Regenerative therapies, however, have become more widely utilized, prompting discussions regarding their evidence base, medical necessity, and appropriate indications. The increase in publications on regenerative medicine in interventional pain management journals, the establishment of dedicated regenerative medicine journals, accredited training programs, and the introduction of board certification, most notably by the American Board of Interventional Pain Physicians (ABIPP), demonstrate the field's growing legitimacy. ABIPP's competency certification in regenerative medicine is recognized in several states as a certifying standard for interventional pain management (2,5-7,17-23,38,55).

Chronic spinal pain is a complex and multifactorial condition, with low back pain being the most prevalent presentation. Its high prevalence, diverse treatment options, and associated social and economic burdens continue to shape medical decision-making. Lumbar intervertebral discs, facet joints, sacroiliac joints, ligaments, fascia, muscles, and nerve root dura are all known pain generators contributing to low back and lower extremity pain (18-21,39,41,56-63). Kirkaldy-Willis et al (64,65) described the degenerative process as involving multiple structures, introducing the "3-joint complex" concept. Building on this foundation, a functional spine unit approach has recently been developed to guide regenerative medicine injections in managing low back pain (65-68).

Traditionally, interventional pain management has focused on targeting individual pain-generating structures. However, in many regions with limited resources, a more comprehensive, multi-structured approach is used to deliver care that is both practical and accessible. Similarly, regenerative medicine employs a functional unit approach emphasizing the overall function and integration of spinal structures rather than focusing on isolated pathology. Interventional pain physicians, well-versed in image-guided procedures for managing spinal and extremity pain, are ideally suited to integrate regenerative techniques into their practice following appropriate education and training as outlined in these guidelines.

2.2 Objective

These guidelines aim to provide a rational and systematic framework for applying regenerative interventions in managing low back pain. They are based on the best available evidence concerning the effectiveness and safety of regenerative therapies for various types of low back pain, including pain attributed to lumbar muscle dysfunction. The literature underscores the importance of evidence-based practice and the need for regular updates to ensure that recommendations align with current clinical standards. Regenerative therapies in this context refer to minimally invasive techniques involving the targeted placement of injectates near structures affected by pain.

2.3 Application

These guidelines are intended for use across multiple medical specialties but are specifically designed for interventional pain physicians and other practitioners utilizing regenerative therapies. Their primary purpose is to provide patients, clinicians, regulators, and payers with clear, evidence-based information to determine the medical necessity and appropriateness of regenerative interventions.

2.4 Adherence to Trustworthy Standards

In developing these regenerative therapy guidelines, the standards established by the Institute of Medicine (IOM) and the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) were followed (40,42,44,69-72). The NEATS instrument, created and validated by the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse (NGC), serves as a tool to evaluate adherence to best practices in guideline development (70). This process ensures that these regenerative therapy guide-

lines meet the highest standards of reliability, transparency, and evidence-based rigor.

2.4.1 Disclosure of Guideline Funding Source

These comprehensive, evidence-based guidelines for regenerative therapies in managing chronic low back pain were commissioned, prepared, edited, and endorsed by the American Society of Interventional Pain Physicians (ASIPP) without any external funding.

2.4.2 Disclosure and Management of Financial Conflicts of Interest

All panel members disclosed potential conflicts of interest covering the previous 5 years. These disclosures extended beyond financial relationships to include professional experience, clinical practice patterns, academic interests, and promotional activities. Members with identified conflicts were recused from any discussions or sections related to their conflicts and agreed not to engage with industry stakeholders regarding any guideline content before data publication.

2.4.3 Composition of Guideline Development Group

A multidisciplinary panel of experts in chronic pain management and interventional techniques from diverse medical disciplines reviewed the available evidence and developed the recommendations for regenerative therapies. The panel represented both academic and community-based practitioners committed to advancing interventional applications in regenerative medicine.

The group included methodologists such as epidemiologists, statisticians, ethicists, and health services researchers experienced in conducting systematic reviews. Editorial safeguards were implemented to prevent influence from authors with industry funding. The panel was both geographically and professionally diverse, including academicians and practitioners. Of the 35 members participating in guideline preparation, there were 19 anesthesiologists, 1 neurologist, 8 physiatrists, 2 radiologists, 2 scientists/researchers, 2 statisticians, 1 pharmacist, 1 dental surgeon, and 1 graduate student, all actively engaged in clinical care or research related to chronic pain.

2.5 Evidence Review

The evidence-based recommendations for regenerative therapies were developed through a consensus process following a comprehensive review of published literature addressing the use and safety of regenerative treatments for low back pain. The methodology was based on principles of best evidence synthesis, as outlined by the Cochrane Review, and adapted from multiple ASIPP-modified guidelines (73,74).

2.5.1 Grading of Evidence

The grading of evidence and recommendations was based on a modified qualitative approach described by ASIPP (73,74), the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework (75,76), and the AHRQ strength of recommendations methodology (71,72). Table 1 outlines the modified qualitative approach to grading evidence described by ASIPP (73), and Table 2 presents the guide for the strength of recommendations developed using the NEATS instrument (70), as modified by the opioid guideline panel (42) and adapted for this guideline.

The grading system for regenerative therapies in low back pain incorporates evidence from randomized controlled trials (RCTs), observational studies, and other clinical reports, as well as systematic reviews and meta-analyses. This approach defines levels of scientific evidence and provides a structured means for grading both the quality of evidence and the strength of corresponding recommendations (70,75,76). Methods consistent with AHRQ's approach to rating the strength of recommendations were also applied (71,72).

2.5.2 Assessment Based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria

GRADE is a transparent framework for developing and presenting evidence summaries and provides a systematic approach for making clinical practice recommendations (75,76). It is the most widely adopted tool for grading evidence quality and formulating recommendations. GRADE defines 4 levels of evidence, also referred to as certainty in evidence or quality of evidence: very low, low, moderate, and high, as shown in Table 3. Certainty of evidence is assessed based on risk of bias or methodological quality of the studies, imprecision, inconsistency, indirectness, and publication bias. Considering these factors, confidence in the evidence may be increased or decreased. Reasons for adjusting certainty in evidence, either upward or downward, are provided in Table 4.

2.5.3 Outcome Measures

An outcome is considered clinically significant if

Table 1. *Qualitative modified approach to grading of evidence of therapeutic effectiveness studies.*

Level I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials
Level II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate or low-quality randomized controlled trials
Level III	Fair	Evidence obtained from at least one relevant moderate or low-quality randomized trial or Evidence obtained from at least one relevant high-quality non-randomized trial or observational study with multiple moderate or low-quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate or low-quality relevant observational studies
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists

Modified from: Manchikanti L, et al. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (73).

Table 2. *Guide for strength of recommendations as modified for ASIPP guidelines.*

Rating for Strength of Recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation. ASIPP Adaptation: Consensus was achieved that there is high certainty that the net benefit is substantial providing strong recommendation. Recommendation: Strong
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation. ASIPP Adaptation: Consensus was achieved that there is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial. Recommendation: Moderate
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation. ASIPP Adaptation: The consensus achieved that there is potential improvement in certain individuals or groups of patients based on individual professional judgement and shared decision making. Recommendation: Weak

Adapted and modified from: National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (70).

there is a reduction of at least 2 points on pain scales such as the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS), or at least a 50% reduction in pain with improvement in functional status in at least 50% of the treatment group. A positive study is deemed clinically significant and effective if the primary outcome is statistically significant with a *P*-value ≤ 0.05.

2.5.4 Analysis of Evidence

Evidence was analyzed using both qualitative and quantitative evidence synthesis. Quantitative synthesis was performed when applicable using conventional and single-arm meta-analyses. If a recent quantitative analysis had already been performed, it was used without duplication unless new studies were available.

2.5.5 Qualitative Analysis

Qualitative analysis was based on best-evidence synthesis, modified and collated using multiple criteria, including Cochrane Review and United States Preventive Services Task Force (USPSTF) criteria, as illustrated in Table 1 (73). The analysis utilized 5 levels of evidence,

ranging from strong evidence to opinion- or consensus-based recommendations.

2.5.6 Quantitative Analysis

Quantitative analysis was not performed specifically for these guidelines; however, recent publications including quantitative analyses were incorporated into the evidence synthesis.

2.5.7 Assessment and Recommendations of Benefits and Harms

These guidelines describe the potential benefits and harms of regenerative therapies for low back pain and explicitly link this information to specific recommendations.

2.5.8 Evidence Summary of Recommendations

Supporting documents summarize the relevant evidence for regenerative therapies and link this information to the consensus-based clinical recommendations.

2.5.9 Rating or Grading the Strength of Recommendations

For each recommendation related to regenerative therapies, the strength of the recommendation is rated based on benefits and harms, available evidence, and confidence in the underlying evidence, using rating schemes recommended by NEATS (42,70).

2.5.10 Specificity of Recommendations

The guideline recommendations are, as much as possible, specific and unambiguous. They are intended to guide actions that should or should not be taken in various clinical settings for regenerative therapies across diverse patient populations.

2.6 Methodologic Quality and Risk of Bias Assessment

Key aspects of the guideline methodology included transparency and reproducibility of judgments, separating risk of bias from other constructs such as applicability and precision, and evaluating risk for each outcome.

2.6.1 Randomized Controlled Trials (RCTs)

2.6.1.1 Scoring Cochrane Review Criteria

Using Cochrane Review criteria (77), as shown in Appendix Table 1, studies meeting at least 9 of 13 criteria were considered high-quality. Studies meeting 5 to 8 criteria were deemed moderate quality, while those scoring less than 5 were considered low-quality and excluded.

Table 3. *GRADE certainty ratings.*

Certainty	What it means
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

Source: BMJ Best Practice. Evidence-based medicine (EBM) toolkit. Learn EBM. What is GRADE? Accessed 08/20/2024. https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/ (76)

Table 4. *Reasons rate certainty in evidence up or down.*

Certainty can be rated down for:	Certainty can be rated up for:
• Risk of bias • Imprecision • Inconsistency • Indirectness • Publication bias	• Large magnitude of effect • Dose-response gradient • All residual confounding would decrease magnitude of effect (in situations with an effect)

Source: BMJ Best Practice. Evidence-based medicine (EBM) toolkit. Learn EBM. What is GRADE? Accessed 08/20/2024. https://bestpractice.bmj.com/info/us/toolkit/learn-ebm/what-is-grade/ (76)

2.6.1.2 Scoring IPM-QRB Criteria

Based on the Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) criteria for randomized trials (78), as shown in Appendix Table 2, studies scoring less than 16 were considered low-quality and excluded. Studies scoring 16 to 31 were considered moderate quality, and studies scoring 32 to 48 were considered high-quality.

2.6.2 Nonrandomized Studies

2.6.2.1 Scoring for Risk of Bias in Non-Randomized Studies of Exposure (ROBINS-E)

The Risk of Bias in Non-Randomized Studies of Exposure (ROBINS-E) tool (79) was used to assess the risk of bias in estimates from cohort studies evaluating the causal effect of an exposure on an outcome, as shown in Appendix Table 3. Studies that met inclusion criteria and scored 5 or higher were considered high quality. Studies scoring 3 to 4 were classified as moderate quality, while those scoring below 2 were considered low quality and were excluded from the evidence analysis.

2.6.2.2 Scoring for IPM-QRBNR

Based on the Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) criteria (80), as shown in Appendix Table 4, studies meeting inclusion criteria but scoring less than 16 were considered low-quality and excluded. Studies scoring 16 to 31 were regarded as moderate quality, while studies scoring 32 to 48 were considered high quality and included in the evidence synthesis.

2.7 Updating Guidelines

These guidelines for regenerative therapies in managing low back pain will be updated within 5 years or sooner if there are significant changes in scientific evidence, public policy, or reported adverse events, with the next update anticipated before January 2030.

2.8 Consensus Development of Recommendations

A modified Delphi technique was used to achieve consensus on the guideline statements (81,82). This approach minimizes bias associated with group interactions and allows for anonymity among panelists. Panelists without primary conflicts of interest voted on the approval of specific guideline statements using an online survey. Each panelist could also propose edits to the wording of statements and provide clarifying comments regarding the implementation of the guidelines in clinical practice. For inclusion in the final guidelines, each statement required at least 80% agreement among eligible panel members without primary conflicts of interest. Disagreements occurred in some statements where members differed regarding the strength or direction of the recommendation.

2.9 Key Questions

These guidelines focus on the following key questions regarding low back and extremity pain:

1. What is the spinal functional unit describing the pathophysiologic and structural basis of low back pain?
2. What are the available regenerative medicine therapies?
3. Are regenerative medicine therapies effective in treating low back and lower extremity pain?
4. The evidence of effectiveness for the use of intradiscal PRP or bone marrow aspirate concentrate (BMAC) and consensus-based clinical recommendations.
5. The evidence of effectiveness for the use of epidural injections of PRP and derivatives and consensus-based clinical recommendations.
6. The evidence of effectiveness for using intra-articular facet joint injections of PRP and consensus-based clinical recommendations.
7. The evidence of effectiveness for the use of PRP in sacroiliac joint injections and consensus-based clinical recommendations.
8. The evidence of effectiveness for the functional spine unit approach and consensus-based clinical recommendations.
9. What are the current guidelines for biologics?
10. What are the adverse consequences/harms of regenerative therapies?
11. What are the precautions in perioperative management of patients receiving regenerative interventional techniques and antiplatelet and anticoagulant therapy.
12. What are the best preventive and therapeutic strategies to improve outcomes when performing regenerative therapies?

3.0 Impact of Low Back Pain on Health Care

Chronic low back pain imposes a substantial socioeconomic burden worldwide (2,39,41,42,83-85). According to a global burden of disease report, low back pain was the leading cause of years lived with disability (YLD) among 395 diseases, injuries, and impairments, accounting for approximately 64 million YLDs, or 7.4% of total YLDs in 2019 (83-85). A 2023 report by the Centers for Disease Control and Prevention (CDC) (85) indicated that 24.3% of U.S. adults experienced chronic pain during the year, with 8.5% reporting high-impact chronic pain. This represents an increase compared to 2021, when chronic pain prevalence was estimated at 21% and high-impact chronic pain at 6.9% (85).

Economic analyses highlight the financial impact of spinal pain management. Dieleman et al (84) reported that U.S. expenditures on personal health care and public health for spinal pain totaled $134.5 billion in 2016, reflecting a 53.5% increase from $87.6 billion in 2013. Similarly, costs for managing musculoskeletal disorders rose 43.5%, from $183.5 billion in 2013 to $263.3 billion in 2016.

In the United States, national healthcare expenditures are projected to have grown 8.2% in 2024, nearly 3 percentage points faster than the growth in gross domestic product (GDP) at 5.3%, reaching $5.263 trillion compared to $4.866 trillion in 2023 and $4.25 trillion in 2022 (86). This increase occurred despite reductions in service utilization, particularly for interventional procedures (50-52,54), and substantial cuts in physician fee schedules, with payments decreasing by 41% from 2001 to 2025 and projected to reach 45% by 2026 (87-89). These trends may reflect uneven allocation of healthcare funds, with certain sectors and the insurance industry realizing significant profits since the implementation of the Affordable Care Act. The sustained growth in healthcare spending reflects increased utilization of services, goods, administrative costs, and profit margins (86-88), following a period of muted growth during the COVID-19 pandemic. Consequently, the health share of the economy is expected to rise to 18% in 2024, up from 17.6% in 2023. From 2024 to 2033, as the population ages and healthcare demand grows faster than income, annual national health spending is projected to increase by 5.8%, outpacing the projected GDP growth of 4.3%. By 2033, the health share of the economy is expected to reach 20.3%, highlighting a critical challenge in ensuring sufficient funds for adequate healthcare services.

Pain prevalence varies by spinal region, with the low back being the most affected at 43%, followed by the neck at 32% and the thoracic spine at 13% (90). Annual prevalence of low back and neck pain ranges from 22% to 65%, with lifetime prevalence estimated at 84% for low back pain and 67% for neck pain (2,39,41,42). Chronic spinal pain persists in approximately 60% of patients for over one year, despite conservative or surgical treatments (2,39,41,42).

Chronic spinal conditions are strongly associated with physical disability and mental health disorders, including depression, generalized anxiety disorder, and somatization (2,39,41,42,83-85,91,92). Moreover, chronic spinal pain in parents is linked to an increased risk of similar conditions in their children during adulthood (93).

Although some studies have suggested a decline in low back pain prevalence (94), recent evidence indicates rising prevalence across all chronic pain categories, with low back pain remaining the most common (85). This increase parallels growing economic and societal costs, driven in part by the expansion of treatment modalities, including regenerative medicine therapies (1-22,38-42,44,95-134).

4.0 Prevalence of Usage of Health Care Modalities in Managing Low Back Pain

The use of various modalities for treating musculoskeletal and spinal pain has grown substantially, including physical therapy, pharmacologic treatments, interventional techniques, and surgical interventions (1-22,38-42,44,98-139).

4.1 Non-Opioid Pharmacologic Therapies

Non-opioid pharmacologic therapies play a central role in managing low back pain, particularly as efforts continue to address the opioid crisis. Given the variability and complexity of low back pain, multiple non-opioid pharmacologic treatments have been employed to provide effective and safe pain relief.

4.1.1 Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs have demonstrated effectiveness in managing acute low back pain by reducing pain and improving function. Evidence suggests that the route of administration can influence efficacy. In a randomized trial, Khankhel et al (127) found that topical diclofenac gel alone was less effective than oral ibuprofen in improving functional impairment. Combining diclofenac gel with oral ibuprofen did not provide additional benefit, indicating that oral NSAIDs remain more effective for acute low back pain in this setting. Furthermore, combining NSAIDs with paracetamol has shown better outcomes than NSAIDs alone, while paracetamol alone has not demonstrated significant clinical benefit in acute low back pain (128).

Although NSAIDs consistently have shown effectiveness in acute low back pain, their efficacy in chronic low back pain is less clear (129,140). Safety concerns persist, with some studies indicating low but notable risk of adverse events. Concomitant use of myorelaxants may increase the likelihood of side effects (129). Cyclooxygenase-2 (COX-2) inhibitors such as Celebrex and Meloxicam are generally considered safer than nonselective NSAIDs due to a lower risk of gastrointestinal complications. Overall, while NSAIDs are integral to managing acute low back pain, their use should be balanced with potential adverse effects.

4.1.2 Muscle Relaxants

Muscle relaxants are often used when muscle spasm contributes to low back pain; however, their effectiveness and safety remain uncertain. Studies evaluating non-benzodiazepine antispasmodics and benzodiazepines have reported mixed results. A meta-analysis by Cashin et al (130) found that non-benzodiazepine antispasmodics slightly reduced pain intensity at 2 weeks or earlier, but this was not clinically meaningful, and no significant improvement in disability scores was observed. Adverse effects, including nausea, dizziness, and headache, were more frequent with these medications.

Studies assessing the combination of muscle relaxants with NSAIDs also show variable results. Hung et al (131) reported that adding tizanidine to diclofenac did not improve functional outcomes in acute low back pain with sciatica. In contrast, Iliopoulos et al (132) found that a single intramuscular injection of diclofenac combined with Thiocolchicoside led to greater pain reduction and improved mobility compared to diclofenac alone, without increasing adverse effects.

The choice of muscle relaxant may influence outcomes. A randomized trial comparing methocarbamol and diazepam for acute low back pain demonstrated that both agents reduced pain within 60 minutes. Diazepam provided slightly greater pain relief but was associated with a higher incidence of drowsiness (133). Overall, the evidence on muscle relaxants for low back pain remains inconclusive. While some studies indicate short-term benefit, their effect on long-term function is unclear, and further high-quality research is needed to clarify optimal drug selection and dosing.

4.1.3 Antidepressants

Antidepressants have been investigated for analgesic effects in chronic low back pain, particularly when neuropathic mechanisms are implicated. Various classes, including tricyclic antidepressants (TCAs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have shown mixed effectiveness and safety profiles.

While earlier meta-analyses suggested minimal benefit with higher discontinuation rates, more recent studies have evaluated specific antidepressants and classes. Duloxetine, an SNRI at 60 mg daily, significantly reduced pain intensity and improved quality of life, although higher doses (120 mg) increased adverse events (135). Other antidepressants, such as amitriptyline, escitalopram, bupropion, imipramine, and desipramine, showed small or inconsistent effects (135). A network meta-analysis by Ma et al (141) ranked TCAs as most effective for pain relief, followed by SNRIs, which also improved functional outcomes. However, both SNRIs and noradrenaline-dopamine reuptake inhibitors were associated with higher risk of adverse effects, including nausea, dizziness, and treatment discontinuation.

Clinicians should carefully weigh risks and benefits before prescribing antidepressants for low back pain, especially in patients without comorbid depression.

4.1.4 Anticonvulsants

Gabapentinoids, including pregabalin and gabapentin, have been widely used for low back pain with neuropathic components, but evidence on their effectiveness is mixed. A meta-analysis of gabapentin and pregabalin for acute sciatica showed limited benefit, with gabapentin improving leg pain but not low back pain or function, and pregabalin showing no significant advantage (142).

Shanthanna et al (143) reported limited evidence of benefit in chronic low back pain, with significant risk of adverse effects, highlighting the need for large, high-quality trials. João et al (144) found gabapentinoids reduced neuropathic pain and sleep interference after spinal cord injury, suggesting a potential minor role for leg pain associated with radiculopathy. Head-to-head comparisons indicated pregabalin may reduce pain more effectively, while gabapentin may provide broader benefits for comorbid symptoms such as anxiety, insomnia, and fatigue (145). Overall, anticonvulsants may provide modest relief in select cases, but their routine use for low back pain is not well supported.

4.1.5 Local Anesthetics

Local anesthetics have been widely used in spinal injections for low back pain (146). Epidural injections combining local anesthetics and steroids have demonstrated efficacy in conditions such as disc herniation, with transforaminal and interlaminar approaches having the strongest evidence, while injections using only local anesthetics or caudal epidurals with or without steroids show moderate evidence (147). Meta-analyses also indicate that lidocaine, with or without steroids, is effective in managing spinal pain from multiple causes (148).

The number of repeat injections required has been examined in several studies. A retrospective study found that transforaminal epidural steroid injections using nonparticulate steroids resulted in a higher proportion of patients not requiring repeat injections within 12 months compared to those receiving particulate steroids (149).

4.2 Non-Pharmacologic and Non-Interventional Techniques in Managing Chronic Pain

Many non-invasive or non-interventional techniques for managing chronic pain include exercise programs, physical therapy, acupuncture, massage, transcutaneous electrical nerve stimulation (TENS), biofeedback therapy, and chiropractic treatment.

4.2.1 Exercise Programs

Structured exercise programs are critical in managing chronic pain. All guidelines, local coverage determinations (LCDs), and medical policies mandate some form of physical therapy and structured exercise programs before employing any interventional techniques or opioid therapy. The CDC guidelines (150) provide high-quality evidence supporting exercise therapy for back pain, fibromyalgia, and hip and/or knee osteoarthritis, demonstrating reduced pain and improved function immediately after treatment, with sustained improvements for 2 to 6 months (150-155). Multiple guidelines recommend aerobic, aquatic, and/or resistance exercises for patients with various types of chronic pain, including osteoarthritis of the knee or hip, back pain, and fibromyalgia (140,156-158). Motor control exercise for low back pain has been reported to be more effective for improving function than minimal intervention (159,160).

Exercise therapy has shown moderate effectiveness in treating chronic low back pain, although no single form of exercise has proven superior. A review of 217 RCTs with 20,969 participants with non-specific low back pain lasting more than 12 weeks concluded that Pilates, McKenzie, and functional restoration approaches were more effective than other exercises in reducing pain intensity and functional limitations (161). A systematic review and meta-analysis of 79 RCTs comparing exercise-based interventions to placebo found that exercise training was more effective than active control or standard medical care in reducing chronic musculoskeletal pain (162).

Morkoç et al (136) evaluated the effects of lumbar stabilization and graded activity exercises on biochemical mediators and clinical outcomes in patients with nonspecific chronic low back pain. Lumbar stabilization exercises increased interleukin-6 (IL-6) concentrations while reducing pain, disability, and catastrophizing. Graded activity exercises increased IL-6 concentrations and reduced pain and disability, but lumbar stabilization exercises were more effective in reducing catastrophizing.

Leininger et al (137) studied the cost-effectiveness of spinal manipulation, exercise, and self-management for spinal pain. spinal manipulative therapy (SMT) was

favorable compared to home exercise and advice (HEA) for acute neck pain (ICERs below $50K/quality-adjusted life year (QALY)) and when added to HEA for chronic back-related leg pain and chronic neck pain in older adults. SMT was likely not cost-effective compared to HEA for chronic back pain in adults or when added to HEA for older adults. SMT compared to exercise therapy in adults with chronic back pain showed favorable outcomes, as did exercise therapy for chronic neck pain in adults and chronic back pain in adolescents (ICERs below $50K per QALY).

Gonzalez-Gomez et al (163) conducted a systematic review with meta-analysis and meta-regression comparing exercise therapy and manual therapy for chronic low back pain. Six RCTs with 743 patients were included. Meta-analysis showed a small but significant long-term benefit of exercise therapy for disability (SMD = –0.25, 95% CI [–0.43, –0.07], p = 0.007). The GRADE assessment indicated very low certainty across outcomes. Exercise therapy may offer small long-term benefits over manual therapy for disability, influenced by sex, age, and treatment duration. The evidence does not strongly support choosing exercise therapy over manual therapy, or vice versa, as a stand-alone treatment.

4.2.2 Physical and Occupational Therapy

Physical and occupational therapy have long been considered supportive modalities for treating acute and chronic pain. Their goals are to reduce pain, improve function, prevent disability, facilitate activities of daily living, and enhance quality of life. A systematic review of occupational therapy interventions for chronic pain recommended individualized techniques and education on biomechanics as essential for therapeutic success (164). An evaluation of 83 studies involving 8,816 patients with chronic low back pain found that exercise therapy reduced pain intensity, disability, and improved long-term function compared to non-exercise conventional care. Behavioral therapy was effective in the short-term for reducing pain intensity (165).

Physical therapy is considered a high-cost treatment option. A randomized trial found no difference in pain intensity, frequency, or disability between patients assigned to low-cost group aerobics versus individual physiotherapy or muscle reconditioning sessions (166). Physical therapy can be particularly helpful for patients who are unmotivated, non-drug compliant, lack access to safe exercise facilities, or have not improved with low-intensity exercise (150). A randomized trial (167) showed that a stepped exercise program combining internet-based exercises, coaching calls, and in-person therapy as needed led to meaningful pain reductions in knee osteoarthritis, with 35% of patients ultimately requiring in-person physical therapy.

The effects of lumbar stabilization and graded activity exercises (136) and the cost-effectiveness of spinal manipulation, exercise, and self-management (137) have been discussed. Insurers often require documentation of recent physical therapy, evidence of adverse effects from therapy, or evidence of a structured exercise program before approving interventional techniques.

4.2.3 Acupuncture

Acupuncture is increasingly used for chronic pain and is the most popular supplemental alternative therapy (168,169). Studies support its use in non-specific musculoskeletal pain (170), osteoarthritis (171), chronic headache (172), and shoulder pain (173). Acupuncture may reduce opioid use (174). In patients with migraines without aura, true acupuncture is associated with long-term reductions in migraine recurrence compared to sham acupuncture (175). Systematic reviews and meta-analyses demonstrate that acupuncture reduces pain in chronic pelvic pain and chronic prostatitis or chronic pelvic pain syndrome (176,177). Trivedi et al (178) concluded that acupuncture is effective for short-term treatment lasting 3 to 5 months.

Guidelines for low back pain differ in recommendations for acupuncture (179-181), based on systematic reviews that show variable effectiveness. Among 16 systematic reviews, 7 showed greater pain relief and functional improvement than no treatment in short-term follow-up; 5 reviews found that acupuncture added to conventional therapy provided short-term improvements in pain and function (182-185). A meta-analysis of 25 studies with 6,200 patients showed significant, although minor, improvements for acupuncture compared to sham treatments and other analgesics (186).

4.2.4 Massage

Massage may relieve pain through physical and mental relaxation and increasing pain thresholds via release of endogenous opioids (187). Mechanisms may include stimulation of large nerve fibers, affecting nociceptive primary afferents and immune cells, and modulation of the autonomic nervous system (188,189). Numerous trials, literature reviews, and meta-analyses have evaluated massage efficacy and/or effectiveness (190-192).

Farber et al (190) found low to very low quality evidence due to study bias and imprecision. Massage improved short-term pain for acute, subacute, and chronic low back pain, with some improvement in function at short-term follow-up. Furlan et al (191) noted that massage was superior to inactive treatments in some studies, similar to exercise in others, and generally better than joint mobilization, relaxation therapy, physical therapy, acupuncture, or self-care education. Benefits persisted up to one year in some cases. Thai massage produced similar results to Swedish massage, and combination therapies showed added benefits.

4.2.5 Transcutaneous Electrical Nerve Stimulation (TENS)

Despite common use, TENS effectiveness is inconclusive. It is not typically covered by insurance and is often restricted to RCT use. Prior assessments found no benefit for chronic pain (193,194). Systematic reviews and meta-analyses (195-198) show little improvement in pain, although some short-term functional benefit may exist. Some evidence suggests TENS reduces pain intensity immediately post-treatment as an adjunct therapy (198,199).

4.2.6 Chiropractic Treatments

Mobilization and manipulation therapies are widely used for chronic pain, though effectiveness, dosing, and safety are debated. It is important to distinguish types and mechanisms of manipulative treatments in osteopathic and chiropractic practice. SMT effectiveness for chronic low back pain is debated; recommendations are heterogeneous. A systematic review by de Luca et al (200) found moderate evidence supporting manual therapy to reduce pain and disability.

SMT is considered first-line in some systems but second-tier after exercise and behavior therapy in others (201,202). Biomechanical theories suggest SMT reduces mechanical stress; neurophysiological theories suggest it engages primary afferent neurons to modulate pain (203-205). Cochrane review evidence indicates SMT provides slight improvement in function, with small to moderate short-term pain relief compared to non-recommended therapies (206). Most adverse events are mild and transient.

Coulter et al (207) found moderate-quality evidence that manipulation and mobilization reduce pain and improve function in chronic low back pain, with manipulation producing larger effects than mobilization. Similar conclusions were reported for chronic nonspecific neck pain (208). Multimodal approaches integrating multiple treatment types may provide the greatest benefit.

RAND studies (209) show that chronic low back pain patients receiving chiropractic care report proactive self-care behaviors and positive clinical experiences. Leininger et al (137) demonstrated favorable cost-effectiveness for SMT with ICERs below $50K per QALY for chronic low back pain.

4.2.7 Biofeedback Therapy

Biofeedback is a psychological treatment that can be performed alone or as an adjunct to interventional and non-interventional approaches, physical therapy, or cognitive behavioral therapy. Patients receive feedback on physiological processes such as respiratory rate, heart rate, or muscle tension and learn to self-regulate these processes (210). Biofeedback types include electromyographic, heart rate variability, respiratory biofeedback, and neurofeedback, with electromyographic and neurofeedback being most common.

Meta-analyses show biofeedback can be more effective than cognitive behavioral or physical therapy (211-213). Sielski et al (213) found that biofeedback produced small-to-medium reductions in pain lasting up to 8 months, while improving depression, disability, muscle tension, and cognitive coping skills. Longer treatments and higher proportions of biofeedback in overall therapy enhanced outcomes. Biofeedback can be used as standalone or adjunctive therapy to improve pain-related outcomes.

4.2.8 Multidisciplinary Rehabilitation

Multidisciplinary approaches are effective, efficient, and ethically appropriate given the multidimensional nature of chronic pain. An RCT of 521 patients with chronic low back pain (214) showed that multimodal non-pharmacological interventions including cognitive therapy, mindfulness, and behavior therapy reduced pain and improved physical function, mood, and sleep.

Multidisciplinary rehabilitation involves coordinated care by clinicians, physical and occupational therapists, mental health providers, and specialists as needed (150,215,216). CDC guidelines support multimodal therapies and biopsychosocial rehabilitation to reduce long-term pain and disability compared to usual care or physical treatments alone. Non-pharmacological therapies can also synergize with non-opioid and opioid medications (150,217). Medications should ide-

ally be combined with non-pharmacologic therapies to optimize outcomes (150).

Multimodal therapies are not always available or reimbursed, and iterative use can be time-consuming and costly, with disparities in access (217). Less intense multidisciplinary rehabilitation can be as effective as high-intensity programs (151), and combinations of medications may be considered within multidisciplinary management. Short and intermediate outcomes show clinical effectiveness, but third-party support for multidisciplinary centers largely disappeared by 2010. Evidence for long-term benefits ranges from small to none (140,151,218). Recent reviews report insufficient evidence for multi- or interdisciplinary rehabilitation for lumbar radiculopathy (140,215), and Cochrane reviews indicate similar outcomes for patients treated surgically or with multi- or interdisciplinary rehabilitation at 2 years (218).

4.3 Opioids

Opioids are widely used in clinical practice to manage chronic low back pain. As described in ASIPP's opioid guidelines (42), multiple reviews over the years have evaluated opioid use, overuse, abuse, and numerous adverse consequences, including opioid-related deaths. Manchikanti et al (42,219) described a fourth wave of opioid-related deaths, expanding upon the 3 distinct waves previously described by the CDC. This wave began in 2016 and has been steadily increasing due to multiple factors, including misapplication of 2016 CDC guidelines, increased availability of illicit drugs, spillover effects of the COVID-19 pandemic, and policies that have limited access to interventional procedures for chronic pain treatment (Fig. 1) (42,219-221).

The overall trends at the time of this publication are as follows (221):

- Decline in 2024: Provisional CDC data indicate a 27% one-year drop in overdose deaths in the US in 2024 compared to 2023, following a 4% decline from 2022 to 2023.
- Declines across drug types: Reductions were seen across all major drug categories, including opioids, which have been the primary cause of most overdose deaths over the past decade.
- Fentanyl remains a concern: Synthetic opioids, primarily fentanyl, continue to be the most frequently involved substance in overdose deaths, although deaths involving fentanyl decreased by approximately 37% between 2023 and 2024.
- Long-term perspective: Despite recent improvements, opioid overdose deaths in 2023 were nearly 10 times higher than in 1999. More than 645,000 people have died from opioid overdoses since the epidemic began.

Potential causes for the recent decline include:

- Public health response: Expanded investments in prevention, treatment, and harm reduction programs, including increased availability of naloxone.

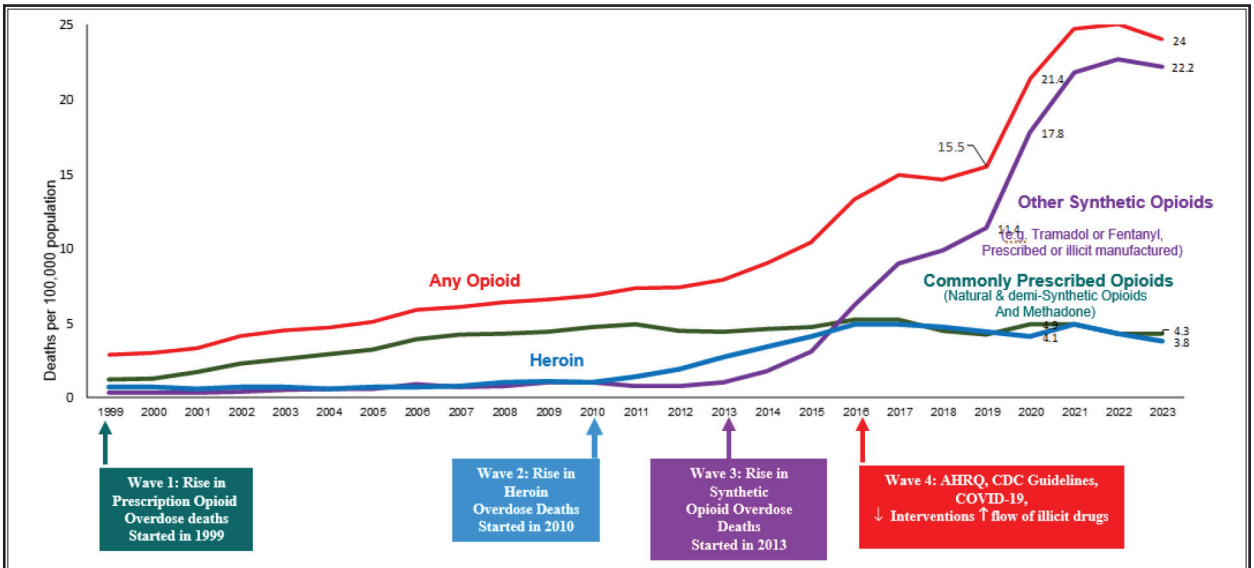


Fig. 1. *Four waves of rise in opioid overdose deaths. Redrawn and modified from CDC figure*

- Weaker street fentanyl: Evidence suggests street fentanyl may be weaker in some areas, contributing to fewer overdose deaths.
- Harm reduction strategies: Increased availability and use of naloxone, which can reverse opioid overdoses, is a critical factor.
- Improved treatment access: Better access to evidence-based treatments, such as buprenorphine and methadone, may also contribute to the decline.

The impact on the population includes:

- Geographic variations: Overdose deaths have disproportionately affected different regions and demographic groups over time. Initially impacting white, rural communities, the crisis increasingly affects Black, Hispanic, and American Indian/Alaska Native communities. West Virginia has the highest overdose death rate per capita.
- Premature deaths: Opioid overdose deaths are a leading contributor to premature mortality, with affected individuals losing an average of 38 years of life.
- Impact on children: Children of individuals with addiction are significantly more likely to develop addiction themselves.
- Healthcare burden: Opioid-related hospitalizations and emergency department visits place a substantial burden on healthcare systems.
- Mental health: The COVID-19 pandemic exacerbated the opioid crisis, increasing substance misuse and worsening mental health.

Multiple efforts to address the opioid crisis include:

- Increased naloxone availability: Naloxone is now available over the counter in most states, with expanded distribution through pharmacies, community programs, and law enforcement.
- Expanded treatment access: Effective treatments for opioid use disorder, such as medication-assisted treatment combining medications with behavioral therapies, are increasingly promoted.
- Prevention and education: Public education about the risks of opioid use and overdose remains essential.
- Addressing health disparities: Targeted interventions are needed to reduce the disproportionate impact on communities of color and other vulnerable populations.

There has been substantial debate regarding the relationship between opioid overdoses and prescription opioid pain relievers, including terminology (42,219,220). Evaluation of the relationship between opioid overdoses, opioid treatment admissions, and prescription opioids in the United States from 2010 to 2019 has been described (220). As shown in Figs. 2 and 3, relationships between total opioid doses, accidental opioid deaths, prescription opioid deaths, opioid treatment admissions, and annual prescription sales (measured in morphine milligram equivalents per capita) are either nonexistent or significantly negative/inverse (222).

4.4 Interventional Techniques

Utilization patterns of interventional techniques have changed substantially over the years, initially showing exponential growth and now showing declines. The COVID-19 pandemic had a lasting impact on

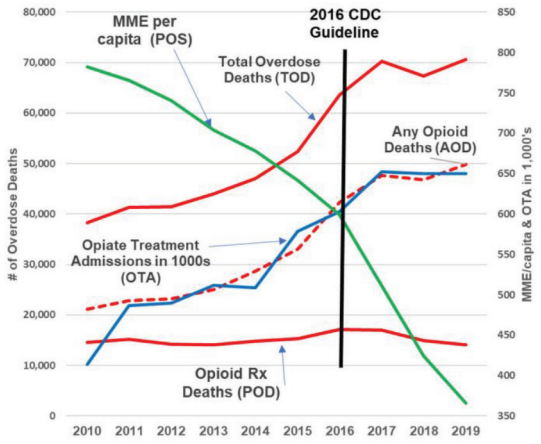


Fig. 2. *2010–2019 update.*
AOD = any opioid overdose death; POD = prescription opioid deaths; POS = prescription opioid sales; OTA = opioid treatment admissions; TOD= total overdose deaths; MME= morphine milligram equivalents
The green line represents opioid prescribing (POS, MME/capita); the red lines are opioid deaths (POD, AOD, and TOD); the blue line represents opioid addiction (OTA). Over the past decade, as the green line (prescription opioids) declined by +50%, prescription opioid deaths remained flat while opioid addiction, any opioid and total overdose deaths continued increasing "exponentially (122)".
Source: Aubry L, Carr BT. Overdose, opioid treatment admissions and prescription opioid pain reliever relationships: United States, 2010-2019. *Front Pain Res (Lausanne)* 2022; 3:884674 (121).

interventional pain management practices (223-226). Analyses showed an 18.7% reduction in interventional technique use for chronic pain in the Medicare population in 2020 (227). Even before the pandemic, growth patterns for interventional techniques were changing and sometimes declining in the Medicare population following the implementation of the Affordable Care Act (ACA) (219,228-231).

In a retrospective cohort study, Manchikanti et al (50) found that interventional pain management services per 100,000 Medicare beneficiaries declined cumulatively by 28.9% between 2019 and 2022, with an annual decrease of 10.7%. This contrasts with 2010-2019, which showed a slight yearly decline of 0.4%. The sharp 18.7% reduction occurred between 2019 and 2020, coinciding with the pandemic. From 2020 to 2021, the decline slowed to 1.1%, then accelerated to an 11.5% drop between 2021 and 2022. Contributing factors likely include COVID-19, economic challenges, the ACA, evolving LCD policies, and insurer medical policies. Figure 4 illustrates usage patterns of interventional techniques.

Similarly, Manchikanti et al (49) showed escalating growth followed by rapid decline in facet joint interventions for spinal pain in the Medicare population. Manchikanti et al (48) reported a 24% decline in epidural procedure visits, and Manchikanti et al (51) showed a 13.5% overall decrease in sacroiliac joint injection procedures post-COVID-19 (2019–2022), averaging a 4.7% annual decline.

4.5 Surgery

Since the first discectomy for disc herniation (misidentified as a "chondroma") by Mixter, a neurosurgeon, and Barr, an orthopedic surgeon, in 1932 (232), surgical treatments for spinal pain have evolved with multiple techniques and a general trend toward increasing surgical interventions, raising questions about treatment effectiveness (233).

The Spine Patient Outcomes Research Trial (SPORT) collected surgical data prospectively (234), demonstrating increasing national trends in surgical interventions (104,123,125,138,235-246), although most data are from 2015. Best et al (138) reported a 460% increase in intervertebral disc disorder surgeries and a 910% increase in spinal stenosis surgeries from 1994 to 2006. Yoshihara and Yoneoka (125) showed a 2.4-fold population-adjusted increase in surgical intervention for degenerative disc diseases from 2000 to 2009. Bae et al (104) reported a 45% increase in lumbar spinal stenosis surgeries and a 1.9% decrease in lumbar decompressions from 2004 to 2009. Martin et al (236) reported a 62.3% increase in elective fusions, with the largest increase (138.7%) in patients aged 65 or older from

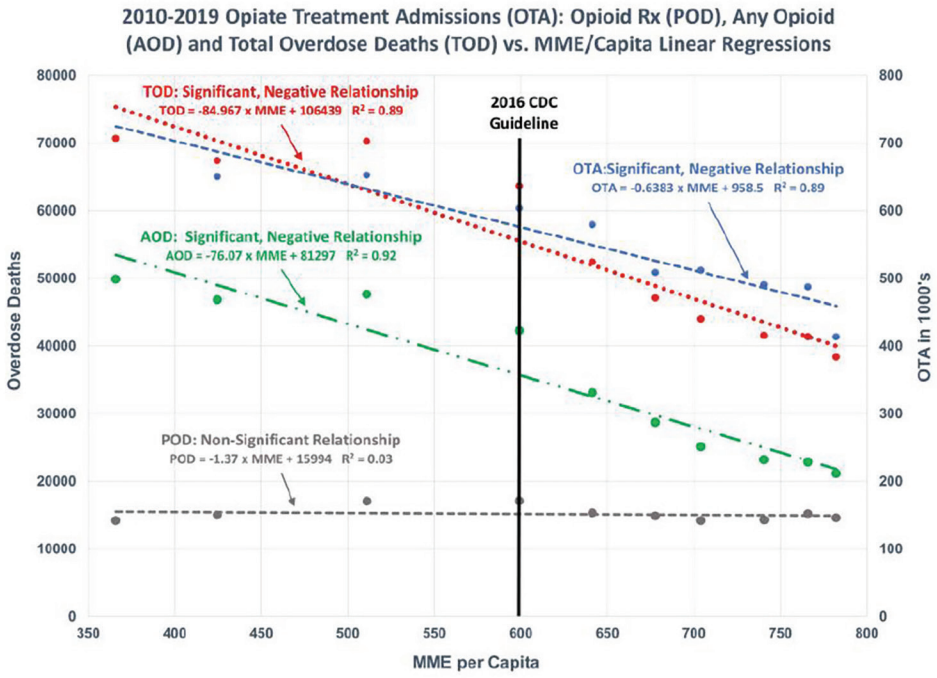


Fig. 3. *2010–2019 regression models: Illustrates the regression of opioid treatment admissions.*
OTA = opioid treatment admissions; POD = prescription opioid deaths; AOD= any opioid overdose death; TOD = total overdose deaths; POS = prescription opioid sales Significant, negative relationships were found for OTA, AOD, and TOD. No significant relationship exists between POD and POS. Source: Aubry L, Carr BT. Overdose, opioid treatment admissions and prescription opioid pain reliever relationships: United States, 2010-2019. *Front Pain Res (Lausanne)* 2022; 3:884674 (121).

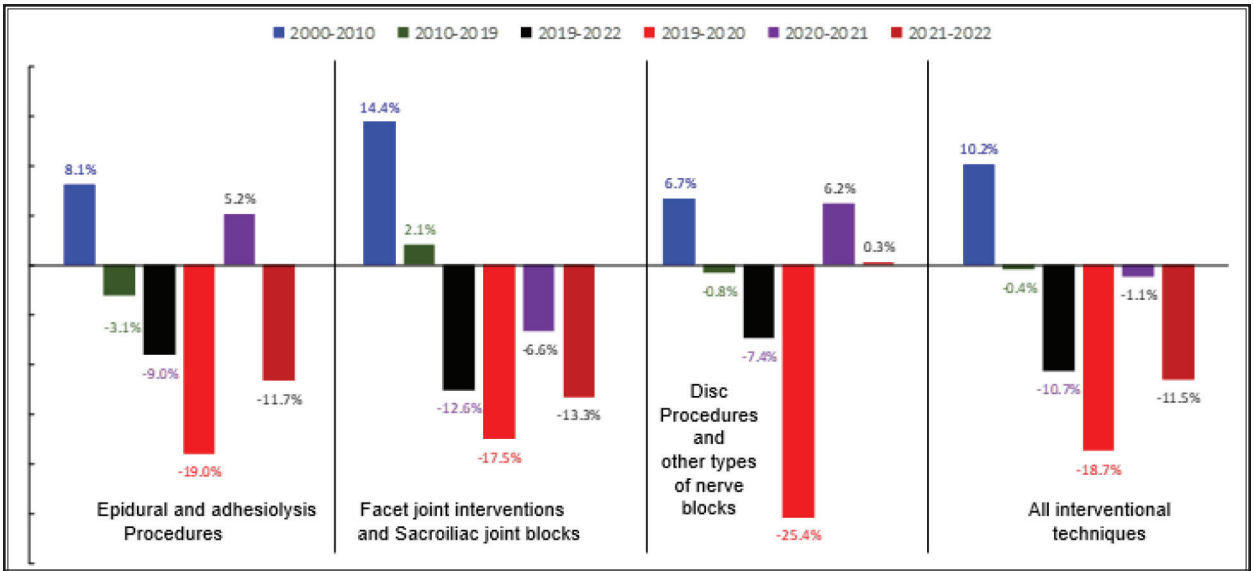


Fig. 4. *Comparative analysis of rate (per 100,000 Medicare recipients) of usage patterns for epidural and adhesiolysis procedures, facet joint interventions and sacroiliac joint blocks, disc procedures and other types of nerve blocks, all interventional techniques (geometric average annual change in rates).*

2004 to 2015, and aggregate hospital costs rose 177%, exceeding $10 billion in 2015.

Lopez et al (235) reported a 24.2% increase in surgical interventions for chronic pain from 2012 to 2017. Re-operation rates for disc herniation and spinal stenosis ranged from 10% to 23% (104), with 40% of post-operative patients developing post-surgery syndrome or failed back surgery syndrome requiring additional treatments (104,240-246). These patients often need multiple modalities, including physical therapy, drug therapy, interventional techniques, complex fusions, and neuromodulation techniques (103,104,113,114,247-261).

Clinicians should ideally exhaust low- to moderate-risk treatments before considering surgery. A retrospective analysis of over 75 million individuals by Kim et al (262) found that nonadherence to clinical guidelines in newly diagnosed low back pain contributed substantially to healthcare costs. Notably, 38.7% of surgical patients did not receive conservative management (physical therapy or epidural steroid injections), accounting for $265 million in healthcare expenses in the first 12 months after diagnosis (262). This highlights the need for careful consideration of surgical interventions to optimize outcomes efficiently.

5.0 Functional Spine Unit: Pathophysiologic and Structural Basis of Low Back Pain

Key Question 1. What is the spinal functional unit describing the pathophysiologic and structural basis of low back pain?

Multiple structures in the low back have been identified as potential sources of specific pain patterns. However, structures proven to cause pain through precision diagnostic blocks include the intervertebral disc, zygapophyseal (facet) joint, sacroiliac joint, and spinal nerves, while degenerative disc disease is typically diagnosed by imaging. Based on precision diagnostic blocks, Manchikanti et al (57), Schwarzer et al (58,263,264), and DePalma et al (265) have reported the prevalence of internal disc disruption or discogenic pain in 26% to 42% of patients, facet joint pain in 27% to 40% of patients with false positive rates of 27% to 47% using a criterion standard of 80% or greater pain relief (41), and sacroiliac joint pain in 2% to 18% of patients. Despite these findings, not all back pain could be accounted for through precision diagnostic blocks or imaging studies. Consequently, it has been postulated that multiple spinal structures contribute to the degenerative process, as described by Kirkaldy-Willis et al (64,65) in their 3-joint degeneration hypothesis.

Effective management of spinal pain and musculoskeletal disorders depends on accurate diagnosis and the use of evidence-based, cost-effective therapeutic interventions. Traditional interventional pain management has largely followed a narrow "pain generator" model, focusing on limited structural targets for temporary rather than disease-modifying effects (18-21,39,41,56-63). The advent of regenerative injection techniques has broadened this perspective, expanding from isolated pain sources to encompass the entire osteoligamentous complex, referred to as the functional spinal unit (FSU) (7).

Over 5 decades ago, White and Punjabi introduced the concept of the FSU, describing each of the 24 spinal levels in the cervical, thoracic, and lumbar regions as integrated mechanisms providing stable structural support for the body (66). The FSU, or spinal motion segment, represents the smallest unit that reflects the functional characteristics of the spinal column. It consists of 2 vertebrae, the intervertebral disc (IVD), zygapophyseal (facet) joints, and the supporting ligaments, including the ligamentum flavum, supraspinous, interspinous, anterior longitudinal, and posterior longitudinal ligaments (Fig. 5) (67,263,266). The IVD and paired facet joints form a 3-joint complex that enables motion between adjacent vertebrae while facilitating load transmission (68). This model incorporates multiple tissue types, fascia, muscles, synovial joints, and ligaments, as integral elements of spinal function and treatment.

Segmental instability, often due to ligamentous laxity or degenerative disc height loss, frequently precedes pain and predisposes individuals to progressive injury as stress and inflammation accumulate across related structures (266,267). Spinal ligaments serve as passive stabilizers that link adjacent vertebrae and restrict movement within safe physiological limits to protect neural structures. Composed primarily of collagen with varying levels of elastin, proteoglycans, and water, these ligaments contribute significantly to spinal stability. The paraspinal muscles, including the multifidus, erector spinae, and psoas major, play an equally important dynamic role in lumbar stabilization. Muscle atrophy and fatty degeneration are frequently seen in patients with chronic low back pain, emphasizing the vital function of these stabilizers in the management of degenerative spinal conditions (10).

A solid understanding of spinal biomechanics is fundamental to identifying the pathogenesis of spinal diseases and the contributions of each bony and soft tissue component to overall spinal stability. In a study evaluating the role of posterior elements in the mechanical integrity of the human L4-5 FSU, these components contributed 24–30% of compressive stiffness and 42–54% of torsional stiffness. The apophyseal joints were found to significantly influence both compressive and torsional stiffness of the L4-5 FSU (268). Ligaments stabilize the spine by restricting excessive motion, while facet joints guide motion and limit shear and torsional forces. Ligament stiffness and mechanical responses vary by age, disc level, and degree of degeneration.

Disc degeneration alters vertebral and facet joint geometry, thereby changing segmental motion behavior (269). A study employing finite element and response surface modeling found that variables such as gender, age, weight, and height significantly influence FSU movement. Overweight or obesity was shown to markedly affect FSU biomechanics, with greater impact in males and older individuals, potentially compromising quality of life (270).

The principal functions of the FSU can be summarized as follows:

1. Stability: Provides support for maintaining spinal integrity and body weight distribution.
2. Mobility: Allows flexion, extension, lateral bending, and rotation through coordinated disc and facet joint movement, preventing excessive motion.
3. Load Bearing: Distributes stresses encountered during daily activities, with the IVD absorbing shock and minimizing vertebral stress.
4. Protection of Neural Structures: Shields the spinal cord and nerve roots through a stable vertebral and ligamentous framework.

5.1 Components of the Functional Spine Unit

5.1.1 Facet Joint

The lumbar facet joints are the only true synovial joints of the spine, formed by articulation between the medially oriented superior articular process of the lower vertebra and the smaller, laterally oriented inferior articular process of the upper vertebra. These diarthrodial joints consist of aneural hyaline cartilage covering the articular surfaces (Fig. 6) (271). The capsular ligament encasing the joint is composed of dense, parallel collagen fibers interwoven with elastic fibers, providing essential resistance to shear and tensile forces during motion (272-275). The subchondral bone, synovium, synovial folds, and joint capsule receive extensive innervation via the medial branch of the dorsal ramus, contributing to both proprioception and nociception (274). Pain from the facet joints may refer to the lower back, lateral hip, posterolateral thigh, groin, or, less commonly, the leg and foot.

Facet joints regulate spinal motion and absorb up to 25% of the load transmitted through the 3-joint complex. Symmetry between joints is essential; asymmetry predisposes to instability and accelerates degeneration of both facets and discs. Under degenerative conditions, facet load bearing can nearly double, leading to progressive deterioration (276). Chronic remodeling and ligamentous weakening are major contributors to degenerative spondylolisthesis (68). Lumbar facet joints have been implicated in 27% to 40% of low back pain cases, with false positive diagnostic rates of 27% to 47% using the 80% pain relief criterion standard (41). Chronic mechanical stress and joint capsule deformation stimulate nociceptors, perpetuating pain (41,57,59,277).

5.1.2 Intervertebral Disc

The intervertebral disc (IVD) is an avascular structure

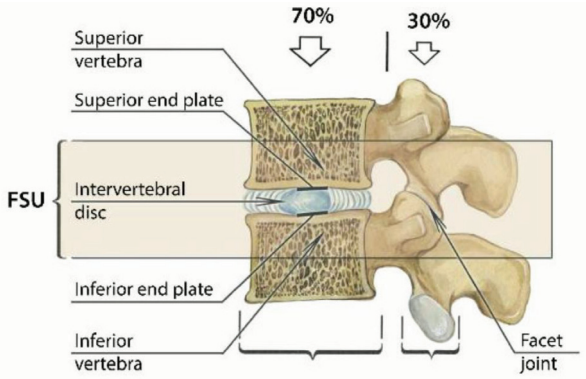


Fig. 5. *Functional spinal unit embodies the two vertebra, intervertebral disc, paired facet joints and the adjacent ligaments.*
Source: Kushchayev SV, Glushko T, Jarraya M, et al. ABCs of the degenerative spine. *Insights Imaging* 2018; 9:253-274 (266).

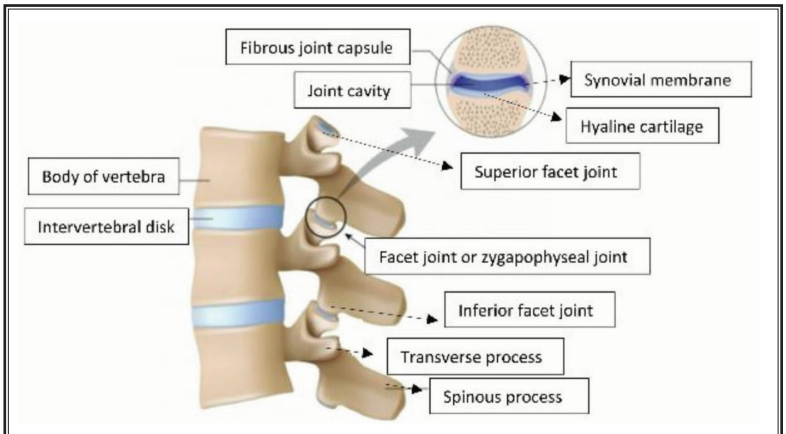


Fig. 6. *Lateral view of the lumbar spine showing vertebral bodies, intervertebral disc and facet joints. A closer look (top right) at the facet joint anatomy displaying the joint cavity along with the joint capsule, hyaline cartilage and synovial membrane.*
Source: Nisolle ML, Ghoundiwal D, Engelman E, et al. Comparison of the effectiveness of ultrasound-guided versus fluoroscopy-guided medial lumbar bundle branch block on pain related to lumbar facet joints: a multicenter randomized controlled non-inferiority study. *BMC Anesthesiol* 2023; 23:76 (271).

composed of a central nucleus pulposus surrounded by concentric lamellae of the annulus fibrosus (Fig. 7) (60,61,277-281). Sandwiched between cartilaginous endplates that facilitate metabolic exchange, the IVD functions in a hypoxic and acidic microenvironment (282-286). Disc homeostasis relies on a delicate equilibrium between anabolic and catabolic activities. Anabolic factors include TGF-α, BMP, GDF5, and IGF, whereas catabolic processes involve enzymes and inflammatory mediators such as IL-1 and TNF-α (284). Degenerative disc disease is characterized by loss of proteoglycans, hydration, and disc height, with resultant redistribution of mechanical load to vertebral bodies and facet joints.

Degenerated discs exhibit reduced compressive height, lessening ligamentum flavum tension but shifting stress to posterior elements. Multilevel degeneration further increases stress on ligaments and pedicles, while non-contiguous degeneration lessens localized stress. These biomechanical variations explain differences between symptomatic and asymptomatic degenerative findings (285).

5.1.3 Vertebral Endplate

The vertebral endplate is a critical structure mediating nutrient transport and biomechanical stability between the vertebrae and IVD (287). Its porosity supports nutrient diffusion, while its rigidity maintains structural integrity. Degeneration and calcification impair nutrient delivery, leading to progressive disc degeneration. Age-related reductions in proteoglycan and collagen content cause thinning and calcification of the endplate cartilage. A strong correlation exists between Modic changes on MRI and discography-confirmed discogenic pain, reinforcing the endplate's role in chronic low back pain.

5.1.4 Sacroiliac Joint

The sacroiliac joint, the largest axial joint in the body, connects the sacrum and ilium, transmitting forces between the spine and lower extremities. It comprises an anterior synovial component and a posterior syndesmosis reinforced by interosseous and posterior ligaments (Fig. 8) (288). The sacrotuberous ligament extends from the sacrum to the ischial tuberosity, while the sacrospinous ligament attaches from the sacrum and coccyx to the ischial spine (289). The joint surfaces, hyaline cartilage on the sacrum and fibrocartilage on the ilium, form an L-shaped articulation allowing minimal multidirectional

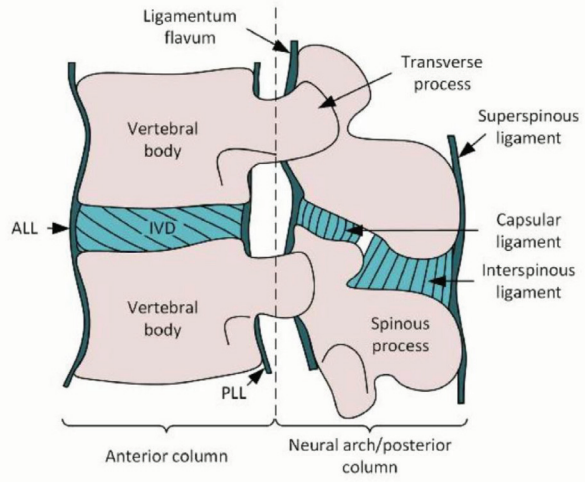


Fig. 7. *Graphical representation of a motion segment; sagittal view. ALL and PLL refer to the anterior and posterior longitudinal ligaments, respectively. The capsular ligament encloses the zygapophysial joint.*
Source: Newell N, Little JP, Christou A, Adams MA, Adam CJ, Masouros SD. Biomechanics of the human intervertebral disc: A review of testing techniques and results. *J Mech Behav Biomed Mater* 2017; 69:420-434 (281).

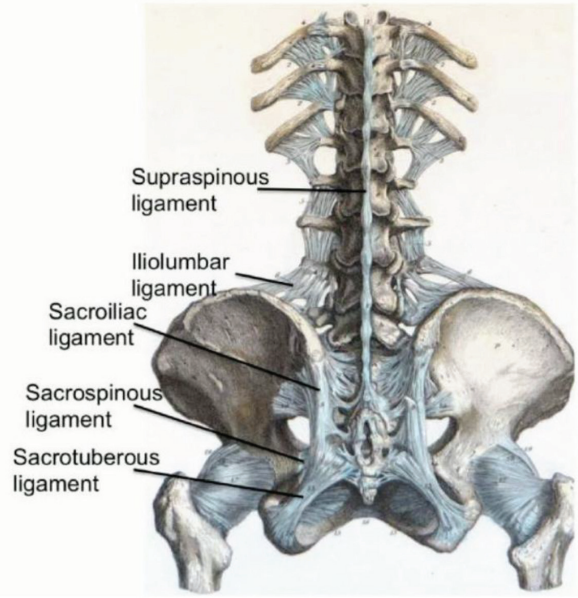


Fig. 8. *Posterior view of the ligaments surrounding the sacroiliac joint.*
Source: Bock CE. In: *Hand-Atlas der Anatomie Des Menschen.* Berline, Verlag, 1860 (288).

motion, approximately 2 degrees across flexion-extension, rotation, and translation planes (290,291).

5.1.5 Spinal Muscles and Ligaments

Spinal stability depends on the integrated action of IVDs, ligaments, and muscles (Fig. 9) (292). While discs and ligaments provide intrinsic stability, muscles supply dynamic support. The principal ligamentous groups include:

1. The anterior and posterior longitudinal ligaments, preventing hyperextension and hyperflexion, respectively.
2. The interspinous and supraspinous ligaments, connecting adjacent spinous processes.
3. The intertransverse ligaments, linking transverse processes to maintain lateral stability.
4. The ligamenta flava, connecting laminae of adjacent vertebrae to preserve spinal flexibility and alignment.

The iliolumbar ligaments anchor the L5 transverse process to the sacrum (293), while the sacrotuberous and sacrospinous ligaments reinforce the sacroiliac joints (289). Paravertebral muscle atrophy, confirmed in both animal and human MRI studies, has been causally linked to chronic low back pain and discogenic changes (294,295). Fatty infiltration and muscular degeneration compromise spinal stability, heighten stress on the facets and discs, and perpetuate a cycle of pain and structural degeneration.

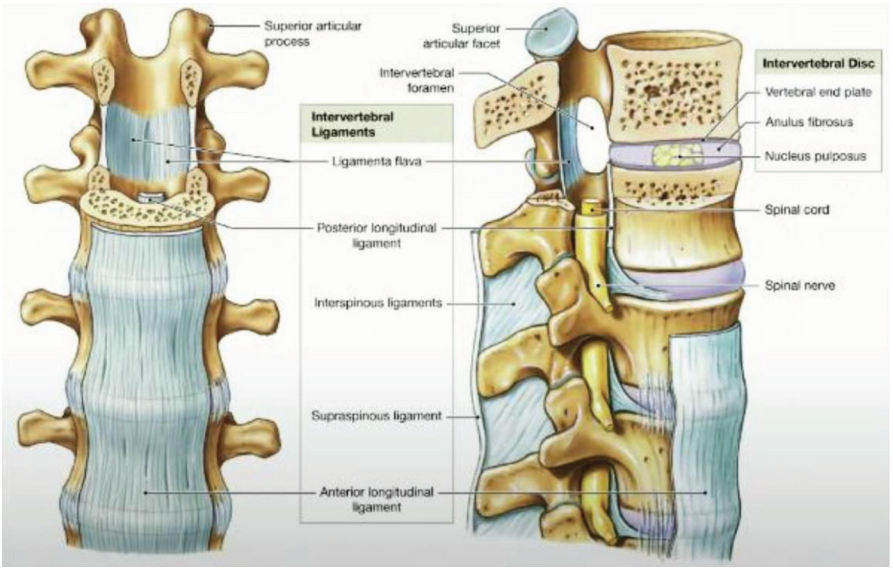


Fig. 9. *Anterior view (left) and lateral view (right) of the vertebral ligaments stabilizing the lumbar spine.*
Source: Marieb EN. In: *Human anatomy & physiology*. United Kingdom, Pearson Education, Limited, 2003 (292).

6.0 Regenerative Medicine

Key Question 2. What are the available regenerative medicine therapies?

Biological therapies promote the healing of damaged tissues either acutely or chronically, including ligaments, menisci, articular cartilage, tendons, intervertebral discs, and joints. Among the various biologicals used in regenerative therapy for the spine and other musculoskeletal disorders, PRP and multipotent mesenchymal stem cells (MSCs) currently serve as the mainstays of regenerative medicine treatment.

Of all the recent innovations in medicine, none have generated as much attention as regenerative medicine. Since their discovery approximately 50 years ago, MSCs have been extensively researched, resulting in over 55,000 published scientific papers and nearly 1,000 completed clinical trials (1,296). Furthermore, more than 5,000 registered clinical trials on www.ClinicalTrials.gov (297) emphasize the growing exploration of MSCs in therapeutic applications. Controlled clinical trials have treated over 10,000 patients (296-300), reporting minimal complications associated with these therapies. It is further estimated that between 10,000 and 70,000 patients have received MSC-based treatments in commercial clinics (2,4,22,23,298,301,302). MSCs are widely recognized for their transformative potential in medicine, particularly in clinical areas with limited therapeutic options. Consequently, the European Medicines Agency (EMA) classifies them as Advanced Therapeutic Medicinal Products (ATMPs), underscoring their importance in modern therapeutic strategies.

The most common use of regenerative medicine today lies in musculoskeletal disorders, particularly with autologous PRP and bone marrow concentrate (BMC) for the treatment of spinal and joint pain. Unlike allogeneic or culture-expanded stem cells, these autologous therapies are permitted by the FDA, enabling clinical application. Numerous clinical trials, especially those involving the knee, have demonstrated the safety and effectiveness of these biologic interventions (302).

6.1 Platelet-Rich Plasma (PRP)

PRP is a concentrate of whole blood that is centrifuged to isolate plasma enriched with platelets and growth factors. In the United States, PRP has FDA approval for use in ligament grafting and bony matrix approximation during reconstructive procedures. The therapeutic benefits arise from an elevated concentration of platelet-derived growth factors released in response to inflammation, such as platelet-derived growth factor (PDGF). These growth factors play an essential role in healing by enhancing fibroblast and osteoblast metabolic activity, reducing cell apoptosis, promoting angiogenesis to improve tissue perfusion, and increasing expression of procollagen genes and collagen-related growth factors, thereby improving the tensile strength of regenerating tissue (18-24,303-312).

PRP contains platelets, leukocytes, and red blood cells, with platelets serving as the central mediators of anabolic effects through the release of growth factors stored in their alpha granules (308). Notable platelet-derived growth factors essential to tissue repair are shown in Table 5 (313-316). Proteins that promote cell proliferation include endothelial growth factor, PDGF, vascular endothelial growth factor (VEGF), and basic fibroblast growth factor (b-FGF). Inhibitory proteins such as b-FGF2 are equally important in preventing over-proliferation (310), although the optimal balance between these proteins remains uncertain. Since each individual produces unique relative concentrations of these proteins, the effectiveness of concentrating autologous platelets for personalized therapy is still being studied.

Therapeutic PRP is recommended to have a platelet concentration at least 2.5 times greater than that of peripheral plasma. Lower concentrations are likely sub-therapeutic, whereas excessively high concentrations may suppress osteoclastic activity (304). PRP formulations vary significantly (309). A meta-analysis identified 14 different treatment indications and 9 unique preparation systems used across clinical studies (317). Consequently, several classification systems have been proposed to categorize PRP based on platelet, leukocyte, and fibrin content, as well as the use of exogenous activators.

Dohan Ehrenfest et al (318) developed a classification system based on leukocyte concentration and fibrin structure. In a comprehensive 2025 review, Zhang et al (298) summarized the active ingredients of PRP and provided a similar classification, outlined below:

- Pure PRP (PPRP) lacks leukocytes and has a low-density fibrin network.
- Leukocyte-rich PRP (L-PRP) has high white blood cell and platelet concentrations with a low-density fibrin network.
- Pure platelet-rich fibrin (P-PRF) is leukocyte-free but has a high-density fibrin network.
- Leukocyte- and platelet-rich fibrin (L-PRF) contains

abundant leukocytes and a high-density fibrin network.

Preparations with a low-density fibrin network (PPRP and L-PRP) are injectable and commonly used for musculoskeletal applications, whereas those with a high-density fibrin network (P-PRF and L-PRF) form a clot containing growth factors within the fibrin matrix (318).

DeLong et al (319) introduced the PAW (Platelets, Activation, White Blood Cells) classification, which organizes PRP formulations based on platelet count, presence of activators, and leukocyte concentration. Although PRP terminology remains inconsistent and no universal classification is accepted, clinicians should be aware of the specific components in any PRP preparation being administered. The American Academy of Orthopaedic Surgeons (AAOS) (320) identified key obstacles limiting PRP advancement and issued consensus recommendations for future research, summarized in Table 6 (320). Factors influencing PRP growth factor composition, related to donor variability, preparation methods, and delivery, are listed in Table 7.

The DEPA (Dose of injected platelets, Efficiency of production, Purity of PRP, Activation of PRP) classification was introduced to refine PRP characterization. Another system, MARSPILL, proposed by Lana et al (321), includes the following parameters: Method, Activation, Red blood cells, Spin, Platelets, Image guidance, Leukocytes, and Light activation.

The platelet-poor plasma fraction also contains bioactive substances, including fibrinogen, alpha-

Table 5. *Function of growth factors stored in platelet-rich plasma.*

Growth Factor	Function
PDGF	Stimulates cell proliferation, chemotaxis, and differentiation Stimulates angiogenesis
TGF-β	Stimulates production of collagen type I and type III, angiogenesis, re-epithelialization, and synthesis of protease inhibitors to inhibit collagen breakdown
VEGF	Stimulates angiogenesis by regulating endothelial cell proliferation and migration
EGF	Influences cell proliferation and cytoprotection Accelerates re-epithelialization Increases tensile strength in wounds Facilitates organization of granulation tissue
bFGF	Stimulates angiogenesis Promotes stem cell differentiation and cell proliferation Promotes collagen production and tissue repair
IGF-1	Regulates cell proliferation and differentiation Influences matrix secretion from osteoblasts and production of poteoglycan, collagen, and other noncollagen proteins

Abbreviations: PDGF = platelet-derived growth factor; TGF-β = transforming growth factor-β; VEGF = vascular endothelial growth factor; EGF = epidermal growth factor; bFGF = basic fibroblast growth factor; IGF-1 = insulin-like growth factor-1.
Adapted and modified from: Refs. (313-316)

Table 6. *Consensus statements on platelet-rich plasma.*

1	Nomenclature and classification system that encompasses autologous blood-plasma products and categorizes preparations in a sufficient detail to facilitate comparison across studies is not available. • A widespread system must be developed with involvement of academics, clinicians, and industry representatives
2	Quality assessment with influence of donor variance and processing and delivery factors on the composition of PRP must be established
3	A validated assay of the efficacy of PRP should be established for each clinical application. • Specific formulationis of PRP should be matched with specific pathologic indicationis. • Methods for establishing proof of safety and efficacy of PRP should be determined. This process may require evidence of phenotype stability or viability for each indication.
4	The relationship between PRP compositioni and efficacy may be established. • Minimum standards of reporting for all studies (preclinical and clinical) evaluating PRP must be established to facilitate communication and the interpretation and synthesis of scientific investigations. These standards must include measured characteristics of the PRP, factors relating to the donor, processing, and delivery of the PRP and outcome parameters.

PRP = platelet-rich plasma
Adapted from: LaPrade RF, Dragoo JL, Koh JL, et al. AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *J Am Acad Orthop Surg* 2016; 24:e62-e78 (320).

Table 7. *Variables that may influence the growth factor profile of platelet-rich plasma.*

• Donor
  • Age
  • Gender
  • Comorbidities
  • Concurrent medications (including anti-inflammatories)
  • Nutritional status

• Processing
  • Blood collection and storage conditions
  • Spin protocol (speed, time)
  • Activation protocol (agent, concentrationi, timing)
  • Storage

• Delivery
  • Form of delivery (gel, solution)
  • Timing of delivery in relation to isolation
  • Timing of delivery in relation to activation
  • Host factors (similar to donor factors)
  • Injury chronicity

Adapted from: LaPrade RF, Dragoo JL, Koh JL, et al. AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *J Am Acad Orthop Surg* 2016; 24:e62-e78 (320).

2-macroglobulin, and exosomes, which have regenerative potential but are beyond the scope of this discussion.

Berrigan et al (312), in a systematic review and meta-analysis, evaluated the effect of platelet dose on outcomes following PRP injections for musculoskeletal conditions. Their findings suggested a potential dose-response relationship, identifying an optimal threshold of greater than 10 billion platelets for favorable results in knee osteoarthritis. This dose appeared to have a stronger effect on functional outcomes than on pain relief. Most studies have focused on intraarticular knee injections, examining PRP dosage, frequency, type, and use of activators (322). Multiple studies support multiple PRP injections rather than a single treatment (323,324) and favor leukocyte-poor over leukocyte-rich PRP (325).

The injection volume also influences outcomes. Typical intraarticular doses range around 4 mL, as most PRP systems yield 3–5 mL (322). However, Kon et al (326) and Patel et al (327) used 8 mL in their studies, and Dhillon et al (328) referred to this as "superdose PRP," recommending it for knee osteoarthritis. Hahn et al (329) demonstrated a positive, dose-dependent effect of PRP on human chondrocytes, while another study confirmed similar dose-dependence on human MSCs (330). Bansal et al (331) found that an absolute platelet count of 10 billion was critical for sustained therapeutic efficacy. Patel et al (322) compared conventional versus "superdose" PRP (8 mL) in early knee osteoarthritis and found significantly greater improvements with the higher dose, though the study was criticized for methodological limitations and lack of imaging. Bennell et al (332) in a 2017 RCT concluded that methodological heterogeneity prevents definitive conclusions about PRP effectiveness in osteoarthritis and called for further high-quality trials.

In a 2025 publication, Rath et al (333) provided a comprehensive review on PRP isolation, activation, and clinical application, presenting a unified framework for optimizing PRP in musculoskeletal repair. They emphasized the urgent need for standardized protocols to improve reproducibility and clinical outcomes. Banu and Sharun (334) proposed minimum reporting requirements for PRP research, including platelet, white blood cell, and red blood cell concentrations. However, outcomes in degenerative spinal conditions remain challenging to interpret (18-21).

The process of PRP preparation introduces inherent variability, as factors such as blood draw volume, centrifugation time, and number of spins affect composition. Even the definition of PRP is debated, while the FDA defines it as containing at least 250,000 platelets per microliter, others suggest a minimum between 1 and 1.5 million platelets per microliter (335). This variability contributes to differences in platelet, leukocyte, and growth factor content among preparations. The 2017 Minimum Information for Biologics in Orthopedics (MIBO) guidelines established standardized parameters for reporting biologics in orthopedic research, including platelet concentration, leukocyte differential, and injection volume (336). Despite these efforts, no uniform injection regimen has yet been defined.

Prior studies have highlighted substantial heterogeneity in PRP research regarding composition, preparation methods, dosage, injection protocols, and rehabilitation strategies (337-340). Platelet dosage, defined as the total number of platelets delivered, calculated by multiplying platelet count, injection volume, and total number of injections, is one key variable affecting outcomes. Everts et al (341) underscored the role of platelet dose in promoting angiogenesis and tissue repair through microvascular regeneration, although few studies have directly examined how platelet dosing influences PRP efficacy across pathologies.

6.2 Mesenchymal Stem Cells (MSCs)

Stem cells represent the foundational versions of cells, capable of differentiating into one or more specialized cell types. Embryonic stem cells possess both pluripotency, the ability to differentiate into any cell

type, and self-renewal capacity. Adult stem cells are found throughout mature tissues and are predisposed to generate the specific cell types of that tissue in response to environmental cues (2,342-349). Adult stem cells, initially described by Caplan (343) as "mesenchymal stem cells," have been renamed medicinal signaling cells (MSCs) and are widely recognized as important therapeutic agents in regenerative medicine (343-349), particularly in musculoskeletal and spinal applications. While adult MSCs have a more limited differentiation potential than embryonic stem cells, it is sufficient for many current and emerging therapies in musculoskeletal and spinal medicine.

A key advantage of MSCs is their relative lack of major histocompatibility complex (MHC) class II surface proteins, allowing them to adopt multiple cell fates and reducing the risk of immune rejection during allogeneic transfer (319,350). MSCs residing in the perivascular space as pericytes can migrate to injury sites and differentiate into required cell types, such as osteoblasts, contributing directly to tissue remodeling (319,350).

An important mechanism of MSC action is their "paracrine influence," which can modulate the differentiation of surrounding cells. High concentrations of catabolic cytokines from acute inflammation favor osteoclastic activity, so a shift toward a less inflammatory environment is necessary for MSCs to exert anabolic effects. Evidence supporting this includes: 1) artificially concentrating MSCs to promote osteoblastic activity has been successfully used to prevent graft-versus-host disease, and 2) MSCs are most effective in degenerative conditions with minimal active inflammation (351).

Efforts to standardize MSC nomenclature have been challenging due to variability in isolation, culture, and assay methods, often resulting in complex and inconsistent terminology (2,342). The International Society for Cellular Therapy (ISCT) issued a position statement in 2006 outlining minimum criteria for defining MSCs (352).

Bone marrow-derived MSCs, first described from bone marrow, remain the most commonly utilized adult stem cells and have FDA approval and recommendations for clinical use (2,342). MSCs have since been isolated from multiple tissues, each with distinct advantages and limitations. MSCs from different anatomical sources of the same tissue may vary in yield, immunophenotype, secreted cytokine profile, and proteomic characteristics (320,353-355). For example, cloned MSCs from adipose tissue tend to default to adipogenic differentiation, whereas bone marrow MSCs preferentially differentiate toward osteogenesis, highlighting the importance of tissue origin in therapeutic outcomes (353). Key regenerative pathways mediated by MSCs include osteogenesis, adipogenesis, chondrogenesis (354-357), and fibrinogenesis (358,359), with varying potentials depending on cell source.

Adipose-derived MSCs (adMSCs) exhibit pro-angiogenic properties, making them promising for ischemic or avascular tissues, such as the avascular zone of the knee meniscus. Bone marrow-derived MSCs (bmMSCs) share similar progenitor potential but also possess homing abilities to injury sites via chemoattractants, integrating into host marrow, bone, and cartilage (351).

Adult stem cells are generally scarce, slow-growing, and require appropriate cytokine stimulation to differentiate effectively. Selecting optimal sources, such as red marrow-rich regions of the iliac crest, can yield 95–100% viable cells (319). Laboratory culture can expand MSC populations (360), but no cultured MSC products have received FDA approval to date (2,27,342,361,362). Accordingly, chemically manipulated adipose tissue-derived SVF or cultured SVF products are not FDA-approved. The AAOS (320) provides a consensus statement on stem cell therapy, summarized in Table 8.

Although MSC numbers in BMC are low, growth factors released during bone marrow aspiration enhance therapeutic potential. It is also important to recognize that adult stem cells may carry host-derived genetic mutations, which can persist in differentiated progeny (319). Gene therapy is under investigation to ensure MSC safety and efficacy.

6.2.1 Bone Marrow Aspirate Concentrate (BMAC)

Autologous BMAC is a potent biologic therapy widely used in musculoskeletal medicine in the United States. BMAC contains platelets, erythrocytes, leukocytes, endothelial progenitor cells, and MSCs, with MSCs representing only 0.001–0.01% of the aspirate but contributing critically to therapeutic effects. BMAC also contains regenerative factors, including VEGF, IGF-1, FGF-1, TGF-β1, IL-1 receptor antagonist protein (IRAP), and alpha-2-macroglobulin (A2M) (363). The combination of MSCs and growth factors confers anti-inflammatory, immunomodulatory, anti-apoptotic, angiogenic, anti-microbial, anti-fibrotic, and regenerative properties.

BMAC offers practical advantages: ease of extraction, minimal manipulation, and immediate clinical

Table 8. *Consensus statements on stem cell therapy.*

1	It is essential to identify the factors contributing to tissue development, regeneration, and healing in each specific tissue. • The mechanisms regulating these contributions must be characterized.
2	The optimum preparation of stem cells for each indication must be established in a systematic fashion. • Considerations should include cell number, concomitant use of growth factors, predifferentization, and vehicle. • Mesenchymal stem cells isolated from different tissues must be compared to identify the most appropriate cell source for each specific indication
3	The mechanism responsible for therapeutic effects observed in applications and appropriate outcome parameters must be established. • A standardized assay of stem cell efficacy is needed. • Methods for establishing proof of safety of stem cell therapy should be determined in collaboration with industry and regulatory agencies. This process may require evidence of phenotype stability or viability. • The most appropriate control for clinical studies evaluating stem cell therapy in each indication must be identified. • The most appropriate, replicable outcomes must be established.

Adapted from: LaPrade RF, Dragoo JL, Koh JL, et al. AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *J Am Acad Orthop Surg* 2016; 24:e62-e78 (320).

use, aligning with the FDA "same surgical procedure" exception (21 CFR 1271.15(b)). The posterior iliac spine provides the highest concentration of MSCs, and optimized aspiration techniques, multiple puncture sites, low volume, rapid aspiration, improve MSC yield (7,364,365). Patient outcomes correlate with MSC quantity, and image guidance via fluoroscopy or ultrasound enhances procedural safety and accuracy. MSC numbers decline with age, particularly in epiphyseal regions, but remaining MSCs generally suffice for therapeutic efficacy.

Clinical studies have demonstrated BMAC effectiveness in lumbar intervertebral disc degeneration (7,364), joint arthritis, avascular necrosis, non-union fractures, and rotator cuff tears. Long-term follow-up indicates that intraosseous BMAC injections for knee osteoarthritis may provide therapeutic benefits lasting up to 15 years (366). Importantly, autologous BMAC has not been shown to promote cancer (367). Standardized protocols, image guidance, and adherence to FDA regulations are essential for safe and effective BMAC therapy.

6.3 Adipose-Derived Stem Cells

Adipose tissue is an abundant source of multipotent stem cells, known as adipose-derived mesenchymal stem cells (adMSCs), first identified in 2001 (368). Adipose tissue contains a heterogeneous cell population: approximately 70% adipocytes, with the remainder comprising endothelial cells, mural cells, fibroblasts, immune cells, preadipocytes, and blood cells (369,370). Tissue from the inner and outer thighs contains higher adMSC concentrations than tissue from the abdomen, waist, or inner knee, and deeper adipose layers yield higher stem cell counts with less fibrous tissue (371).

6.3.1 Types of Adipose Tissue Used in Medical Therapies

Adipose tissue preparations for regenerative therapy include macrofat, microfat, nanofat (372), and SVF, each with distinct structural and cellular properties.

Macrofat consists of adipose globules greater than 2 mm, retaining tissue architecture, vascular structures, and a complete cellular population. Microfat is obtained via small-perforation liposuction cannulas or mechanical fragmentation using a 1.2 mm micronizer, largely preserving connective tissue, vascular elements, adipocytes, and cellular microenvironment. Nanofat is derived from microfat through mechanical emulsification (400–600 micron), retaining a regenerative microenvironment with adMSCs, preadipocytes, endothelial cells, pericytes, macrophages, lymphocytes, and smooth muscle cells within a collagen scaffold. SVF (373) is obtained via enzymatic digestion of adipose extracellular matrix, yielding a heterogeneous single-cell population including adMSCs, endothelial progenitor cells, pericytes, macrophages, and other immune and stromal cells.

Adipose tissue contains significantly higher progenitor cell concentrations than bone marrow, with approximately 5–10% adMSCs (374) versus 0.001–0.01% bmMSCs (375). The abundant availability, ease of extraction, higher stem cell concentration, low senescence, and potent regenerative potential make adipose tissue an advantageous source for regenerative therapies.

6.3.1.1 Biological Activity and Therapeutic Potential

Processed adipose tissue exhibits a rich secretome including proliferative, angiogenic, anti-apoptotic, and differentiation-promoting factors such as PDGF, VEGF, IGF, and HGF. Anti-inflammatory and immunomodula-

tory proteins are also present, including TGF-β1, IL-4, IL-6, IL-10, IL-1RA, prostaglandin E2, NO, SDF-1, IDO, and extracellular vesicles/exosomes (370,376,377).

6.3.1.2 Clinical Applications

Microfat and nanofat have expanded clinical utility in regenerative medicine, demonstrating positive outcomes in wound healing (378) and musculoskeletal disorders, including osteoarthritis (379,380), tendon injuries (381), and ligament damage. Usuelli et al (381) reported nanofat injection for Achilles tendinopathy was safe and more effective than PRP, leading to faster and superior tissue repair. Multiple studies confirm the safety and efficacy of autologous microfat and nanofat in knee osteoarthritis, with meta-analyses supporting their therapeutic potential (382). AdMSCs also show promise for femoral head osteonecrosis (383,384), with mechanisms involving chondrocyte proliferation, inflammation modulation, and angiogenesis.

6.3.1.3 Regulatory Considerations and Advantages

Microfat and nanofat therapies are autologous, minimally manipulated through mechanical processes, and suitable for immediate point-of-care application, consistent with the FDA "same surgical procedure" exception (21 CFR 1271.15(b)) (36).

6.3.2 Adipose Tissue-Derived Stromal Vascular Fraction

Autologous SVF for musculoskeletal applications is obtained via enzymatic digestion of lipoaspirated adipose tissue (385). Mechanical isolation methods have been reviewed (386), but enzymatic digestion remains more common due to higher cell yield (387,388). SVF has been primarily applied in knee osteoarthritis (9 studies) with limited use in wound care (2 studies), discogenic low back pain (1 study), femoral head avascular necrosis (1 study), and jaw reconstruction (1 study) (389). No serious adverse events were reported, with minor harvest site discomfort, edema, soreness, or ecchymosis resolving spontaneously (390). Higher SVF cell counts correlated with improved outcomes in knee osteoarthritis (391,392), with greater benefits in KL Grade III versus Grade IV knees (393).

6.4 Exosomes

Exosomes, or small extracellular vesicles (sEVs), mediate intercellular communication (394,395), are secreted by nearly all cell types, and are present in most body fluids. They exhibit low immunogenicity and are considered a "cell-free" regenerative therapy. Exosomes carry proteins, lipids, DNA, and RNA reflective of the source cell (396). MSC-derived exosomes replicate the paracrine effects of their parent MSCs, including immunomodulation, angiogenesis, tissue proliferation, and antimicrobial activity (360,397). Exosomes present in PRP, SVF, and BMC contribute to their therapeutic effects. Purified exosome preparations have been studied in vitro and in animal models for intervertebral disc degeneration (398) and peripheral nerve regeneration (399,400). Few clinical trials on ClinicalTrials.gov currently investigate MSC-derived exosomes for musculoskeletal pathologies (395). Challenges remain in scaling cGMP exosome production and defining optimal dosing and treatment intervals.

6.5 Non-Autologous Biologics

Non-autologous biologics (NABs) used in regenerative therapy include placental tissues, amniotic fluid, cord blood/tissue, cadaveric-derived tissue, and cultured cells (401). NABs containing viable cells or substantially altered tissues require FDA approval (401). Products not requiring approval include dehydrated human amniotic/chorionic membrane (dHACM) sheets, which have shown accelerated wound healing in diabetic ulcers (402) and pediatric burns compared to split-thickness skin grafts (403). Recently approved NABs include cultured human cells on scaffolds for deep partial-thickness burns, achieving 83% wound closure by month 3 (401,404). Most commercially available injectable NABs derived from amniotic fluid, amniotic tissue, or cord blood/tissue remain unapproved by the FDA (401).

6.6 Other Commercially Available Biologic Preparations

While a variety of regenerative products exist, including autologous and allogeneic culture-expanded MSCs, exosomes, amniotic fluid, amniotic membrane, and umbilical cord tissue, only autologous PRP and BMC are currently FDA-compliant for clinical use in spinal and joint conditions. Although non-approved donor-derived products may have regenerative potential, limited evidence supports their safety and efficacy.

FDA restrictions have not prevented companies from marketing non-approved regenerative products, often failing to meet manufacturing standards and causing serious infectious complications. The FDA has issued warning letters and consumer alerts regarding these practices (405). Widespread use of unapproved products by illegitimate stem cell clinics has raised

significant safety and legal concerns (406), with consequences including lawsuits, regulatory action, warning letters, settlements, medical board sanctions, and, in some cases, criminal penalties.

Preliminary data suggest some non-approved products may provide benefits in musculoskeletal pain management (407); however, use of these therapies is not recommended until further research is conducted and FDA approval is obtained, ensuring patient safety and treatment efficacy.

7.0 Effectiveness of Biologic Therapy in Chronic Low Back Pain

Key Question 3. Are regenerative medicine therapies effective in treating low back and lower extremity pain?

The components of the 3-joint theory of spinal degeneration include intervertebral disc degeneration and facet joint loading and degeneration, which may result in spinal deformity, nerve root compression, and potentially central canal and/or foraminal stenoses (2,64). Regenerative treatments for low back pain have emerged due to the suboptimal outcomes of conventional therapies and growing interest in disease-modifying approaches. Platelet-rich plasma (PRP) and stem cells represent 2 promising regenerative therapies currently applied in the management of low back pain, with or without radiculopathy.

Diagnostic studies have identified the intervertebral discs, zygapophysial (facet) joints, and sacroiliac joints as the most common sources of low back pain (2,18-21,39,41,56-63). Discogenic pathology, with or without internal disc derangement, is estimated to account for 16.9% to 39% of chronic low back pain cases without radiculopathy. Lumbar disc disorders may manifest as disc prolapse, protrusion, extrusion, or herniation (60). Symptomatic lumbar disc herniation occurs in approximately 1% to 3% of the population, while lumbar radiculopathy and sciatica are estimated at 0.98% (2,18-21,39,41,56-64). The lumbosacral facet joints are also recognized contributors to chronic low back and referred lower extremity pain. Controlled studies indicate that facet joints generate low back pain that is neither radicular nor discogenic in 16% to 41% of cases (41,277). Similarly, studies using controlled diagnostic blocks have implicated the sacroiliac joints in 10% to 25% of low back pain cases without disc herniation, discogenic pain, or radiculitis (408).

Pain arising from disc degeneration, disc herniation, or facet and sacroiliac joint pathology may resolve spontaneously in some patients. However, a significant proportion develop chronic pain requiring more advanced treatment approaches. Many clinical decisions in the management of these disorders are not supported by randomized controlled trials or high-quality observational studies (409).

Consequently, alongside traditional management strategies, there has been a paradigm shift toward a functional spinal unit (FSU) approach for regenerative medicine injections in low back pain, rather than relying solely on precision diagnostic and therapeutic techniques (28). Regenerative medicine represents a shift from conventional interventional pain management, which predominantly uses precision diagnostic blocks to identify specific pain generators and targets a limited set of structures as temporary measures, toward a disease-modifying approach (8,10,28).

Several cell-based therapies have been proposed, including injections of MSCs or PRP. Evidence supporting these therapies has been developed in basic science research and translated into clinical studies through controlled trials.

The current literature includes systematic reviews, randomized controlled trials, and numerous observational studies. Evidence is strongest for intradiscal biologic treatments but is emerging for facet joint injections, epidural injections, and sacroiliac joint injections. Additional evaluations have been conducted using a spine FSU approach, considering treatments targeting multiple structures, as well as literature regarding injections into ligaments and muscles.

7.1 Intradiscal Injections

Key Question 4. The evidence of effectiveness for the use of intradiscal PRP or bone marrow aspirate concentrate (BMAC) and consensus-based clinical recommendations.

Intervertebral disc degeneration, a primary contributor to discogenic pain, is driven by neuroinflammation-induced nociceptive fiber innervation within the disc (60,61). The intervertebral disc consists of the nucleus pulposus, annulus fibrosus, and cartilaginous endplate, providing structural support and shock absorption. Degenerative changes disrupt these functions, resulting in lumbar spine instability.

Conventional treatments do not halt the degenerative cascade or promote regeneration (60,61,111,279). Mechanisms implicated in disc degeneration include the loss of stem and progenitor markers, extracellular matrix imbalance, increased inflammation, sensory hyperinnervation, vascularization, and dysregulated signaling pathways. In response, regenerative therapies such as MSC and PRP injections have emerged as promising options (2,6,17,95,107-111,279-283,400).

Preclinical and clinical studies increasingly support the efficacy of MSCs and PRP for discogenic low back pain. These findings have been evaluated through controlled trials and systematic reviews (10,410-420).

A search for intradiscal regenerative medicine in-

jections, including PRP, BMC, or BMAC, was conducted following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (421), consistent with the search methodology of Manchikanti et al (18). This search identified 2 additional studies included in a 2024 systematic review (18). Two randomized controlled trials (RCTs) assessing intradiscal stem cell injections were identified.

Levi et al (422) performed a double-blind, randomized, sham-controlled trial with BMC in 63 patients (48 receiving BMC, 15 receiving sham). The sham procedure involved simulation of intradiscal injection using a 22-gauge needle tapping at the corresponding transverse process and a rapid intramuscular injection of 3 mL of contrast agent. The study concluded that intradiscal BMC was equivalent to the sham procedure for chronic discogenic low back pain, with both groups demonstrating high but statistically comparable success rates. The authors acknowledged significant limitations, including lack of quality cell analysis, which restricted conclusions regarding BMC effectiveness.

Vadalà et al (423) treated 52 patients with chronic low back pain using BM-MSCs or a sham procedure. Although autologous BM-MSC intradiscal injections demonstrated regenerative effects, including significant increases in disc height and other parameters at 3 and 6 months, no differences in clinical outcomes were observed. Accordingly, the systematic review conducted in 2024, incorporating all available studies and reviews, was utilized for further analysis.

More than 10 systematic reviews have evaluated management of discogenic pain with or without disc herniation, including intradiscal injections (18). Sanapati et al (17) reviewed the literature at that time, including 2 clinical reviews on intradiscal biologics (109,110), preclinical studies (107), and spinal conditions such as spinal cord injury, intervertebral disc repair, and spinal fusion (108). Basso et al (109) focused on 7 clinical studies encompassing 104 patients.

Manchikanti et al (18) performed a systematic review and meta-analysis following PRISMA guidelines (421), incorporating methodological approaches from previous reviews and guidelines to enhance rigor (38,39,41,42,44,74,77,98-102). Their analysis included 8 RCTs (11,424-430), 4 evaluating PRP (11,425,427,428), 5 evaluating MSCs (11,424,426,429,430), and 8 observational studies (7,431-437), 4 assessing PRP (431,432,434,435) and 4 assessing MSCs (7,433,436,437). Study characteristics are summarized in Tables 9 and 10. Methodological quality and risk of bias were assessed using standardized measures (Appendix Tables 1, 2, and 4). Dual-arm and single-arm meta-analyses are shown in Figures 10-16.

This review incorporated recent studies on PRP, allogenic MSCs, and homologous BMC. Study quality was high according to Cochrane and Newcastle-Ottawa criteria, and moderate to high using IPM-QRB and IPM-QRBNR. No additional studies were available for inclusion; thus, data from this systematic review were used. Methodological quality, GRADE, and overall certainty were re-evaluated and adjusted. Conventional meta-analysis demonstrated significant pain relief at 24 months and functional improvement at 3, 6, and 12 months. Single-arm meta-analysis showed substantial improvements from baseline at all time points between 1 and 24 months.

Qualitative analysis of intradiscal PRP included 4 RCTs (11,425,427,428), 3 of which were positive trials with moderate certainty. Non-randomized and observational studies were also considered in single-arm analyses, with all 4 studies showing positive outcomes (431,432,434,435). GRADE assessment of RCTs is presented in Table 11. Evidence quality was rated as fair, Level III, with low to moderate certainty and moderate recommendation strength based on qualitative and quantitative analysis.

For MSCs, qualitative RCT evidence showed that 4 of 5 trials were positive (11,424,426,430), with 3 positive trials demonstrating moderate certainty (11,424,430). Two recent studies not included in the systematic review (422,423) were both negative. Among 4 nonrandomized or observational studies, all were positive (7,433,436,437); however, Atluri et al (7) used a functional spine unit model with injections into multiple structures. Conventional meta-analysis including this study showed no significant difference at 3 and 6 months for pain compared to control, but at 12 months the response favored MSCs, which continued through 24 months. Functional status favored MSCs at 3, 6, and 12 months. Single-arm meta-analysis demonstrated favorable responses for MSCs for pain at 3 and 6 months and for function at 3, 6, 12, and 24 months. GRADE assessment using all RCTs is shown in Table 1.

Overall, based on qualitative and quantitative evidence, MSC therapy was deemed Level III, fair, with low to moderate certainty and moderate recommendation strength.

Wu et al (110), in a systematic review and single-arm meta-analysis of 6 studies on cell-based therapies for lumbar discogenic pain, concluded that these therapies were associated with improvements in pain

Table 9. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
PLATELET-RICH PLASMA								
Tuakli-Wosornu et al, 2016 (425) RA, PC, DB Single center Quality Scores: Cochrane = 12/13 IPM-QRB = 37/48	n = 47 Lumbar discogenic pain Selection Criteria: Clinical Evaluation: Imaging and provocation discography Biologic Used: PRP	n = 29 patients in the treatment group Injection of disc levels that elicited concordant pain with evidence of incomplete annular disruption with < 2 mL were injected with 1-2 mL of PRP	n = 18 Injection of disc levels that elicited concordant pain with evidence of incompetent annular disruption with less than 2 mL were injection with 1-2 mL of contrast	FRI & NRS for pain, pain and physical function domains of the SF-36, and the modified NASS Outcome Questionnaire 1, 4, & 8 weeks, 6 months, 1 year	Follow-up rate: 92% 8-week follow up: Significant improvement in pain ($P = 0.02$, function $P = 0.3$) Patient satisfaction ($P = 0.01$) PRP Group: Worst pain decreased from baseline of 7.98 to 5.82. Comparator: 7.72 at baseline and 6.83 One-year follow-up: Significant improvements from baseline to one-year were observed NRS worst pain 2.12-point change ($P < 0.01$) Significant improvement in FRI scores was maintained through one-year from baseline	Well designed, randomized, double-blind control design with a rigorous participation selection process and high follow-up rate and long-term data of at least one-year in the majority of the treatment group Satisfactory results at 8 weeks, 6 months, and one-year	The relief patterns were significant; however, authors have not calculated 50% or greater proportion of patients with the 50% or greater pain relief Data collection in the control group was performed only up to 8 weeks	Positive trial of PRP Intradiscal injections of PRP x 1 showed significant improvement at 8-week follow-up with maintained improvement compared to controls at 1-year follow-up
Navani et al, 2024 (11) RA, PC, DB Multicenter Quality Scores: Cochrane = 12/13 IPM-QRB = 38/48	43 patients were randomized into 3 groups: Placebo = 12 PRP = 15 BMC = 16 Selection Criteria: Imaging, clinical assessment Biologic Used: Intradiscal PRP Intradiscal BMC	Intradiscal PRP injection, 1-2 mL, into the painful disc(s) until resistance to further injection was felt by the operator in the PRP group (n = 15) In the BMC group, 1-2 mL of BMC was injected intradiscally until resistance to further injection was felt by the operator (N = 16)	Patients in the placebo group receive deep trigger point injections with normal saline into the muscle (n = 12)	NRS, patient satisfaction, ODI 1, 3, 6, and 12 months	Significant improvement was seen in PRP and BMC groups at 6- and 12-month follow-up compared to baseline There was no significant difference between PRP and BMC over a 12-month period ($P = 0.094$) ODI was significantly reduced ($P = 0.001$) for both biologic groups Changes in pain scores over 12 months were significant ($P = 0.0043$) ODI scores significantly improved in the crossover group also ($P = 0.0137$)	Multicenter, randomized, controlled trials with crossover design Overall, good results compared to overall appropriate results compared to placebo There were no differences between PRP and BMC group	Placebo group was intramuscular injection with short-term follow-up, randomization blinding	Positive trial of PRP Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC

Table 9 cont. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Goyal et al, 2022 (427) RA, AC Quality Scores: Cochrane = 12/13 IPM-QRB = 37/48	n = 48 patients Selection Criteria: Clinical assessment, imaging, and positive provocation discography Biologic Used: PRP or intradiscal radiofrequency ablation	2 mL of PRP per disc was injected (n = 24)	PIRF ablation was carried out at 70° C for 4 minutes (n = 24)	NRS, ODI 3 months and 6 months Proportion of patients with > 50% reduction in NRS	At 3 months, NRS score was significantly less in radiofrequency group compared to PRP group (P = 0.001) At 6 months, there was no significant difference between NRS and ODI of both groups Both NRS and ODI decreased significantly over 6 months within each group 11 patients in both groups had > 50% improvement in NRS	A prospective, active, controlled trial comparing radiofrequency vs. PRP	Active controlled trial	Negative trial for PRP The response to intradiscal injection of PRP showed 11 of 26 patients responding at 6 months with ≥ 50% relief
Akeda et al, 2022 (428) RA, AC, DB Quality Scores: Cochrane = 13/13 IPM-QRB = 38/48	n = 16 Disc degeneration at L3/4-L5/S1 Selection Criteria: Confirmed using standardized provocative discography Biologic Used: PRPr	n = 8 Intradiscal injection of 2 mL of PRPr into each disc	n = 8 Intradiscal injection of 2 mg in 2 mL saline of betamethasone sodium phosphate	VAS, quality of life, ODI, RMDQ, JOA back pain evaluation questionnaire	VAS scores of both PRPr and corticosteroid group groups decreased significantly (P = 0.01) There were no differences between the groups At week 60, success rate was 87.5% in the PRPr group and 40% in the corticosteroid group. Even then, it was not statistically significant	Randomized, double-blind, active controlled trial	Small sample size. Active control trial	Positive PRP trial Significant improvement at 60 weeks in PRPr group compared to baseline data; however, even though it was different, it did not reach statistical significance in comparison with the steroid group
MESENCHYMAL STEM CELLS								
Pers et al, 2024 (429) RA, PC, DB Multicenter Quality Scores: Cochrane = 10/13 IPM-QRB = 44/48	Randomized patients = 114 BM-MSC group (n =58) Sham placebo group (n = 56) Biologic Used: Intradiscal BM-MSC	Intradiscal injection of 2 mL of 20 million BM-MSCs in injectable-grade Plasma-lyte using a 22G spinal needle	Sham injection without intradiscal puncture consisted of subcutaneous injection in the back of the patient of 2 mL of sterile saline in similar conditions in the surgical theatre	Primary endpoint: Rate of responders defined by improvement of VAS for pain of at least 20% and 20 mm, or improvement of ODI of 20% between baseline and month 12 The secondary structural co-primary endpoint: Change in the disc fluid content measured by quantitative T2 MRI Secondary endpoints: Pain VAS, ODI, SF-36 MCID in all time points of 1, 3, 6, 12 and 24 months	At 12-month follow-up, the study did not demonstrate clinical and imaging benefits and co-primary endpoint was not reached However, at 12-months, the percentage of responders was 74% of patients in the experimental group vs. 68.8% in the placebo group The change in disc fluid content suggestive of disc regeneration between baseline and month 12 was an average of 41.7% in the placebo group vs. 37.9% in the treatment group VAS improved at all points in both groups The proportion of patients reaching MCID in VAS pain score with 30% improvement between baseline and 1, 3, 6, 12 and 24 months were slightly elevated in BM-MSC group but not statistically significant The same result was seen in the proportion of patients reaching the MCID in ODI scores with 10-point improvement No serious adverse effects related to the intervention occurred	The first of its nature DB, RA, multicenter PC trial of allogenic bone marrow-derived mesenchymal stromal cell-based therapy in patients with strict inclusion criteria Data shows procedure is safe This trial provides valuable insights into the complexities of MSC therapy in challenging clinical context	There was no significant difference between treatment group and placebo group	Negative trial of stem cells Comparative analysis of allogenic bone marrow-derived mesenchymal stromal cell-based therapy for patients with chronic low back pain showed that the procedure is safe. However, at 12 months, the study did not demonstrate clinical and imaging benefits as study endpoints did not reach significance There were non-significant improvements in endpoints, VAS, and ODI

Table 9 cont. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Navani et al, 2024 (11) RA, PC, DB Multicenter Quality Scores: Cochrane = 12/13 IPM-QRB = 38/48	43 patients were randomized into 3 groups: Placebo = 12 PRP = 15 BMC = 16 Selection Criteria: Imaging, clinical assessment Biologic Used: Intradiscal PRP Intradiscal BMC	Intradiscal PRP injection, 1-2 mL into the painful disc(s) until resistance to further injection was felt by the operator in the PRP group (n = 15) In the BMC group, 1-2 mL of BMC was injected intradiscally until resistance to further injection was felt by the operator (n = 16)	Patients in the placebo group receive deep trigger point injections with normal saline into the muscle (n = 12)	NRS, patient satisfaction, ODI 1, 3, 6, and 12 months	Significant improvement was seen in PRP and BMC groups at 6- and 12-month follow-up compared to baseline There was no significant difference between PRP and BMC over a 12-month period ($P = 0.094$) The ODI was significantly reduced ($P = 0.001$) for both biologic groups The changes in pain scores over 12 months were significant ($P = 0.0043$) The ODI scores significantly improved in the crossover group also ($P = 0.0137$)	Multicenter, randomized, controlled trials with crossover design. Overall, good results compared to overall appropriate results compared to placebo There were no differences between PRP and BMC group	Placebo group was intramuscular injection with short-term follow-up, randomization blinding	Positive trial of stem cells Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC
Noriega et al, 2017 (426) RA, PC, DB Quality Scores: Cochrane = 11/13 IPM-QRB = 32/48	24 patients with chronic low back pain with lumbar disc degeneration and unresponsive to conservative treatments. Selection Criteria: Clinical and imaging selection criteria Biologic Used: allogeneic bone marrow MSCs	n = 12 The intervention group received allogeneic bone marrow MSCs by intradiscal injection of 25 x 10, 6 cells per segment under local anesthesia	n = 12 A sham infiltration of paravertebral musculature with anesthetic	VAS, ODI, MRI, SF-12 Follow-up = 12 months	MSC-treated patients displayed a quick and significant improvement in all algofunctional indices versus the controls Both lumbar pain and disability were significantly reduced at 3 months and improvement was maintained at 6 and 12 months. Overall, there was an average 28% improvement in pain and disability 1 year after the intervention Only 5 of the 12 outcomes in patients (40%) receiving MSCs were described as perfect treatment with 100% improvement	Well performed RCT with multiple parameters. 100% improvement was seen in 40% of the patients Average improvement was only 28% in pain and disability one year after the intervention	Overall improvement was on average 28% for pain and disability one year after the intervention	Positive trial of stem cells 40% of patients with perfect results 28% improvement in all patients Degeneration improved in MSC treated patients and worsened in the controls. Feasibility and safety were confirmed in this preliminary study

Table 9 cont. *Study characteristics of randomized controlled trials assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Amirdelfan et al, 2021 (424) RA, PC, DB Multicenter Quality Scores: Cochrane = 13/13 IPM-QRB = 36/48	100 participants with chronic low back pain were divided into 3:3:2:2 ratio Selection Criteria: Clinical and imaging assessment Biologic Used: Allogeneic, MPCs from bone marrow from a healthy donor	Allogeneic expanded STRO-3+ MPCs from iliac crest, 2cc per injection 2 groups: 18 million mesenchymal precursor cells + hyaluronic acid (n = 30) 6 million mesenchymal precursor cells + hyaluronic acid (n = 30) hyaluronic acid control (n = 20), or Saline control (n = 20)	2 Groups: Injection of 2 cc hyaluronic acid (n = 20) Injection of saline (n = 20)	VAS, ODI, SF-36	There were significant differences between the control and MPC groups for improvement in VAS and ODI. All study groups showed improvements from baseline at all time points 6 million & 18 million MPC groups showed significant mean VAS score improvement compared with saline at 12, 24, and 36 months and was significant compared with hyaluronic acid at 3 and 6 months for 6 million MPC and at 3 months with 18 million MPC Both MPC groups, were superior at 12, 24, and 36 months to saline	Multicenter, randomized, placebo-controlled, long-term safety and efficacy study	Complicated design and presentation of results making it difficult for replication.	Positive trial of stem cells Positive results with safety and efficacy in a randomized, multi-site trial with multiple variables; however, there were no significant radiographic improvements in any of the groups
Gornet et al, 2024 (430) RA, PC, DB Multicenter Quality Scores: Cochrane = 11/13 IPM-QRB = 34/48	n = 60 Selection Criteria: Clinical evaluation, imaging Biologic Used: Allogeneic disc progenitor cells	Intradiscal biologics Low dose cells n = 20 High dose cells n = 20 Single intradiscal injection of 1 mL into a single symptomatic lumbar intervertebral disc	Vehicle alone (n = 10) Placebo (n = 10) Single intradiscal injection of 1 mL into a single symptomatic lumbar intervertebral disc.	VAS pain improvement > 30% at 12 weeks, ODI, EQ-5D Health Index	At week 52: High dose group had a mean VAS percentage decrease from baseline (62.8%, p = 0.0005), achieving the endpoint of back pain improvement greater than 30%. At week 104: The clinical improvement was maintained in the high dose group. The vehicle group had a smaller significant decrease in VAS (-52.8, p = 0.044) Low dose and placebo group showed non-significant improvements Overall, only the high dose group had a significant change in disc volume at 52 and 104 weeks	This appears to be the first approved biologic therapy, randomized, clinical trial using allogeneic disc progenitor cells to show improvement in pain, disability, and quality of life, along with along with increase in disc volume in patients with lumbar disc degeneration	Small number of patients even though sample size calculations were performed. Further, significant adverse events surprisingly in vehicle or placebo groups.	Positive allogeneic disc progenitor cells trial Significant effectiveness of high-dose allogeneic disc progenitor cells with clinically meaningful improvement in back pain and disc volume at one-year and 2 years

AC = active controlled; BMC = bone marrow concentrate; BM-MSC = bone marrow mesenchymal stromal cell; DB = double-blind; EQ-5D-5L = EuroQol 5 Dimension; FRI = Functional Rating Index; IPM-QRB = Interventional Pain Management techniques – Quality Appraisal of reliability and Risk of Bias Assessment; JOA = Japanese Orthopedic Association; MCID = minimal clinically important difference; MPC = mesenchymal precursor cells; MRI = magnetic resonance imaging; MSCs = mesenchymal stem cells; NASS = North American Spine Society; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; P = prospective; PC = placebo controlled; PIRF = percutaneous intradiscal radiofrequency; PRP = platelet-rich plasma; PRPr = platelet-rich plasma releasate; RA = randomized; RCT = randomized controlled trial; RMDQ = Roland Morris Disability Questionnaire; SF-12 = 12-Item Short Form Health Survey; SF-36 = 36-item Short Form Health Survey; STRO-3 = stromal precursor antigen-3; VAS = Visual Analog Scale

Table 10. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
PLATELET-RICH PLASMA								
Jain et al, 2020 (434) R Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 26/48	25 patients Discogenic pain Selection Criteria: Clinical evaluation, imaging, provocative discography Biologic Used: PRP	PRP injection at a single or multiple disc levels	None	NRS, ODI	At 6-month follow up proportion of patients showing > 50% reduction in NRS was 55%, ODI was 65%. Correlation coefficient between platelet concentration and reduction in NRS and ODI. NRS at 6-months (P = 0.0002) and ODI (P = 0.0006)	Appropriate selection criteria NRS and ODI scores appear to have been significantly reduced Authors carefully evaluated correlation coefficients between platelet concentration (PRP) and reduction in NRS and ODI at different time periods. Further, they also evaluated proportion of patients with greater than 50% reduction in NRS and ODI scores	Relatively small with only 80% of patients being followed.	Positive study of PRP 65% of the patients reported greater than 50% reduction in pain scores with significant reduction in ODI scores (P = 0.0006)
Kirchner & Anitua, 2016 (432) O, R, pilot study Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 27/48	n = 86 Lumbar disc degeneration Selection Criteria: Clinical evaluation, imaging Biologic Used: PRGF-Endoret	One intradiscal, one intraarticular facet, and one transforaminal epidural injection	None	VAS over time 1 month, 3 months, 6 months	Pain reduction after PRGF- Endoret injections showed statistically significant drop from 8.4 ± 1.1 before the treatment to 0.8 ± 1.7 at 6-month follow-up At the end of 6 months, 91% of patients showed an excellent score, with 8.1% showing moderate improvement, and 1.2% were inefficient score group	Reasonably large sample of 86 patients	Only a 6 month follow up The injection was into the disc plus intraarticular and transforaminal epidural injections. Consequently, specificity may have been lost	Positive study of PRP Fluoroscopy-guided infiltrations of intervertebral discs and facet joints with PRGF in patients with chronic LBP resulted in significant pain reduction assessed by VAS The results showed reduction of the VAS over time. The study ended at 6 months with 91% of the patients showing an excellent score, 8.1% showing moderate improvement, and 1.2% showing lack of response

Table 10 cont. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Machado et al, 2022 (435) P, case series Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 25/48	n = 46 Chronic low back pain Selection Criteria: Clinical evaluation, imaging Biologic Used: PRP	1 mL of PRP into each disc. In addition, majority of the patients also received 2 mL for transforaminal injection per site, 5 mL for caudal injection, 2 mL for each facet joint and capsule, and 2 mL for each site of paravertebral muscles	None	VAS, RMDQ	Significant lower scores of RMDQ and pain VAS at weeks 12, 26, 52 in comparison to baseline ($P = 0.001$) Mean VAS pain scores decreased by approximately 35%, RMDQ decreased by 40% at 52 weeks. Opioid consumption was significantly reduced at 52 weeks	Injections of PRP in a prospective case series of multitargets for low back pain	There is no specific structure causing the pain; it was multitargeted and multiple injections with no definitive diagnostic process	Positive study of PRP Significant improvement in pain, function, and opioid consumption
Monfett et al, 2016 (431) P Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 23/48	n = 29 Lumbar discogenic pain, lumbar disc degeneration Selection Criteria: Discogenic Pain Biologic Used: PRP	Injection of PRP	None	Pain relief, functional status 2 years	Statistically and clinically significant improvements in pain and function through 2 years of follow-up	None	A small retrospective evaluation	Positive study of PRP Intradiscal PRP injections show continued safety and improvements in pain and function at 2 years post-procedure
MESENCHYMAL STEM CELLS								
Pettine et al, 2015 (433) P, open-label, NR, 2-arm study Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 30/48	26 patients Selection Criteria: Symptomatic moderate to severe discogenic low back pain Patient age (yrs)= 18–61 years (median 40) Biologic Used: BMC	Autologous bone marrow concentration (nonexpanded) 2–3 mL of BMC was injected in lumbar disc (1.66_106/mL)	None	ODI, VAS, and MRI 3 years	The average ODI and VAS scores were reduced to 22.8 and 24.4 at 3 months After 36 months, 6 patients proceeded to surgery. • After 36 months, 20 of the 26 patients reported average ODI and VAS improvement to 17.5 ± 32 and 21.9 ± 4.4 respectively One year MRI indicated 40% of patients improved one modified Pfirrmann Grade and no patient worsened radiographically	A first prospective evaluation assessing the effectiveness of intradiscal bone marrow publishing long-term follow-up of 36 months. 20 of 26 patients reported improvement	Nonrandomized prospective evaluation without comparative groups Weak data at 3-month follow-up	Positive study of autologous bone marrow At 36-month follow-up, 6 of 26 patients progressed to surgery. The remaining 20 patients (77%) reported significant ODI and VAS improvements Authors concluded that there were no adverse effects, and the study provided evidence of safety and feasibility of intradiscal BMC therapy

Table 10 cont. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Haines et al, 2022 (436) P, cohort study Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 28/48	32 patients Selection Criteria: Provocative discography Biologic Used: BMAC	Intradiscal injection with 1-6 mL BMAC per disc based on acceptance of the volume by the disc	None	VAS back pain, VAS leg pain, ODI, EQ-5D-5L	32 patients were treated with 92 levels VAS back pain decreased by 2.4 points ($P = < 0.001$) from 3 to one-year post procedure VAS leg pain scores decreased by 1.5 points ($P = < 0.005$) ODI scores decreased by 12.4 points ($P = < 0.001$) MCID: VAS back pain 59.4% VAS leg pain 43.8% ODI 56.3% No complications were reported. Three patients went on to have fusion surgery.	Strict selection criteria and methodology with appropriate statistical analysis	Non-randomized, prospective evaluation without control groups.	Positive study of BMAC Improvement was seen in established MCID values, with 59.4% improvement in VAS back pain scores, 43.8% in VAS leg pain scores, and 56.3% in ODI scores Authors concluded that intradiscal injection of autologous BMAC significantly improved low back pain, disability, and quality of life at one-year
Atluri et al, 2022 (7) Open label, P, NR, 2-arm exploratory study Single center Quality Scores: Newcastle-Ottawa = 8/8 IPM-QRBNR = 36/48	n = 80 Selection Criteria: Clinical evaluation, imaging Biologic Used: BMAC	Intradiscal injection of BMC 2 mL, epidural space 2 mL, facet joints 0.5 mL, and sacroiliac joint 1 mL	Conservative management	NRS, ODI, EQ-5D-5L, PROMIS global physical and mental health Follow up 3, 6, and 12 months	Significant improvement at 12-month follow-up with 67% of patients in the study group achieving MCID utilizing ODI, compared to 8% in the control group Greater than 2-point pain reduction was seen in 56% of the patients at 12 months Opioid use decreased in the interventional group	Even though it was an observational, open-label study, it was a prospective controlled study with multiple parameters and outcomes criteria with one-year follow up	All the patients were self-pay, thus, only the patients who could afford the treatment were included Injection was not specifically intradiscal, it was intradiscal intra-facet, epidural, and sacroiliac joint	Positive study of BMC Positive study with significant improvement shown overall at 12 months in 67% of the patients

Table 10 cont. *Study characteristics of non-randomized and observational studies assessing intradiscal biologics.*

Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Lewandrowski et al, 2023 (437) R, O, cohort study Single center Quality Scores: Newcastle-Ottawa = 6/8 IPM-QRBNR = 31/48	n = 33 Degenerative disc disease diagnosed by imaging Selection Criteria: Clinical evaluation, imaging Biologic Used: Biologic allogeneic polyclonal MSC	Intradiscal injection of approximately 5 million allogeneic polyclonal MSCs and 1% hyaluronic acid derived from immunoselected umbilical cord stem cells	None	VAS, ODI, modified Macnab criteria	2-year follow-up, the average VAS low back pain reduction and ODI reductions were significant Macnab outcomes were excellent in 11 patients (33.3%), good in 19 (57.6%), and fair in 39.1% Imaging - Pfirrmann grading was 4.05 ± 0.72 and improved to 3.65 ± 0.81 at final follow-up	Observational study with long-term follow-up Overall, VAS score reduction at 2-year follow-up was 6.565 ± 1.619 ($P < 0.001$). ODI reduction at 2-year follow-up was 38.333 ± 14.865 ($P < 0.001$)	Observational study with a small sample size	Positive study MSCs Favorable outcomes at 2-year follow up

BMC = bone marrow concentrate; BMAC = bone marrow aspirate concentrate; EQ-5D-5L = EuroQol 5 Dimension; IPM-QRBNR = Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies; LBP = low back pain; MCID = Minimal Clinically Important Difference; MRI = magnetic resonance imaging; NR = - nonrandomized; NRS = Numeric Rating Scale; O = observational; ODI = Oswestry Disability Index; P = prospective; PROMIS = Patient Reported Outcomes Measurement and Information System; PRP = platelet-rich plasma; PRGF = plasma rich in growth factor; R = retrospective; RMDQ = Roland-Morris Disability Questionnaire; VAS = Visual Analog Scale

and disability scores. Later, Sanapati et al (17), in a 2018 publication, identified 6 studies, one RCT and 5 observational studies, of which 2 RCTs (425,426) and 2 observational studies (431,432) were included in the present analysis. A single-arm meta-analysis demonstrated significant improvement at 6 months, with high heterogeneity across studies, and a reduction in pain scores from baseline of 40.631 ± 14 points (95% CI: -68.07 to -13.19, $P < 0.0001$, $I^2 = 97.8$). At 12 months, significant improvements were also observed in a pooled sample of 57 patients. Sanapati et al (17) identified 9 publications on cell-based therapies for lumbar discogenic low back pain; among these, one RCT (426) and 3 reports of a single study (364,433,438) were excluded from the present analysis due to small sample size. A single-arm analysis of the 6 available studies, including one RCT and a pooled sample size of 71, demonstrated a reduction in pain scores from baseline to 12 months of 36.943 points (95% CI: -49.855 to -24.030, $P < 0.001$), with high heterogeneity ($I^2 = 86\%$). Functional status also improved significantly at 12 months, with a 26.342-point decrease in disability scores (95% CI: -32.359 to -20.325, $P < 0.001$), with moderate heterogeneity ($I^2 = 55\%$).

Yolcu et al (411), in a 2020 systematic review on MSCs and BMC, included 6 studies with 93 patients. Pain improvement was reported in 38.8% of patients at 3 months, 40.8% at 6 months, and 44.1% at 12 months. Average improvement in Oswestry Disability Index (ODI) scores was 24, 26.5, and 25.7 at 3, 6, and 12 months, respectively. The authors concluded that cell-based therapy may have a potential positive impact. However, the systematic review was limited by small sample sizes, non-randomized study designs, and lack of quality assessment or meta-analysis. They also noted that a 50% success rate for pain improvement was not achieved, although disability scores improved significantly.

Her et al (412), in a 2022 systematic review on intradiscal injections of BMAC and culture-expanded BM-MSCs for discogenic pain, included 16 studies with 607 participants in a qualitative synthesis without data

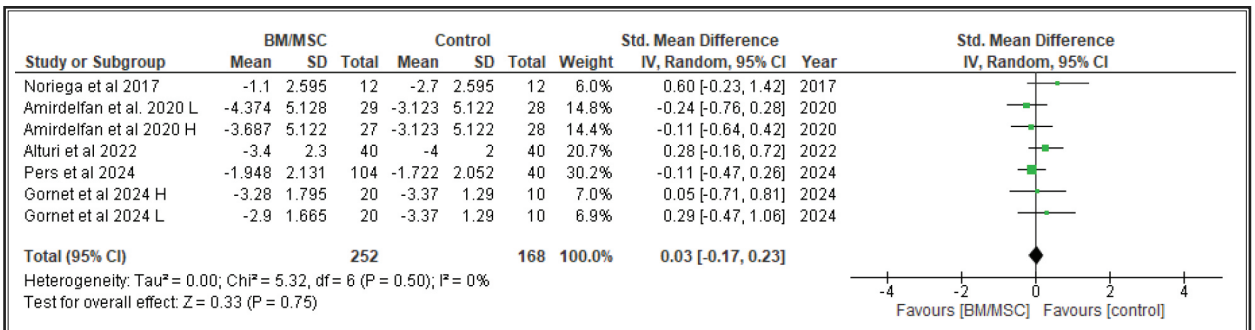


Fig. 10A. *3 Months NRS BM/MSC vs. control.*

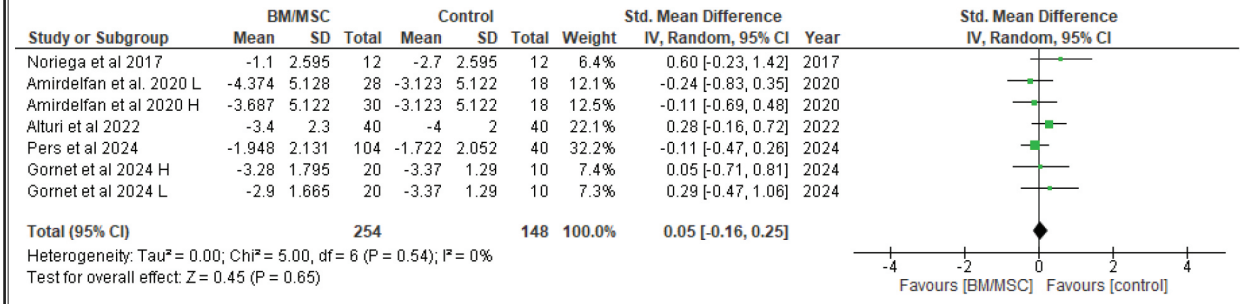


Fig. 10B. *6 Month NRS BM/MSC vs. control.*

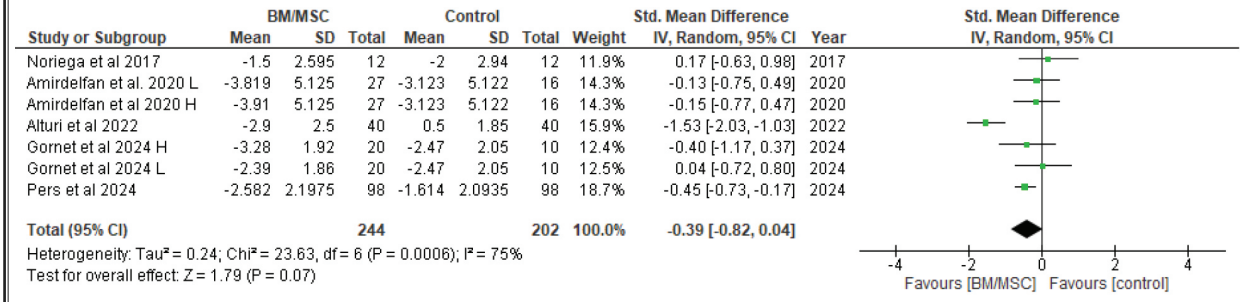


Fig. 10C. *12 Months NRS BM/MSC vs. control.*

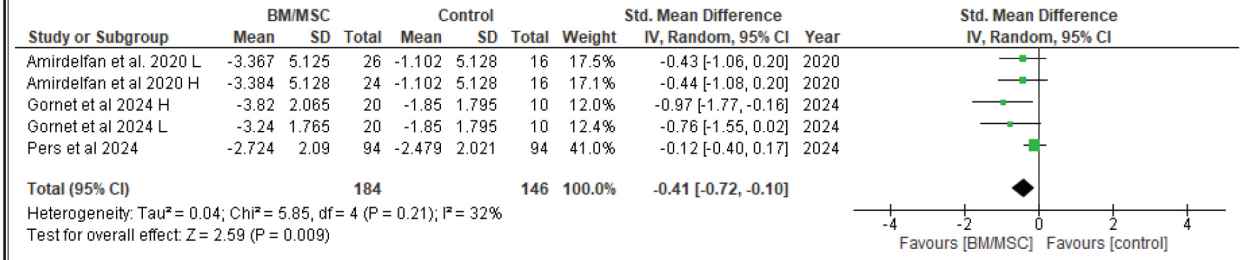


Fig. 10D. *24 Months NRS BM/MSC vs. control.*

Fig. 10. *Conventional analysis of pain relief with intradiscal MSC administration.*

pooling. The studies comprised 3 RCTs, 9 prospective cohorts, 3 case series, and one retrospective study. Studies with fewer than 25 patients or follow-up under 6 months were excluded, leaving 3 studies (426,433,434) for the present review. Her et al (412) reported that intradiscal autologous or allogeneic BMAC and BM-MSCs generally improved discogenic pain and physical function, with some positive anatomical changes on

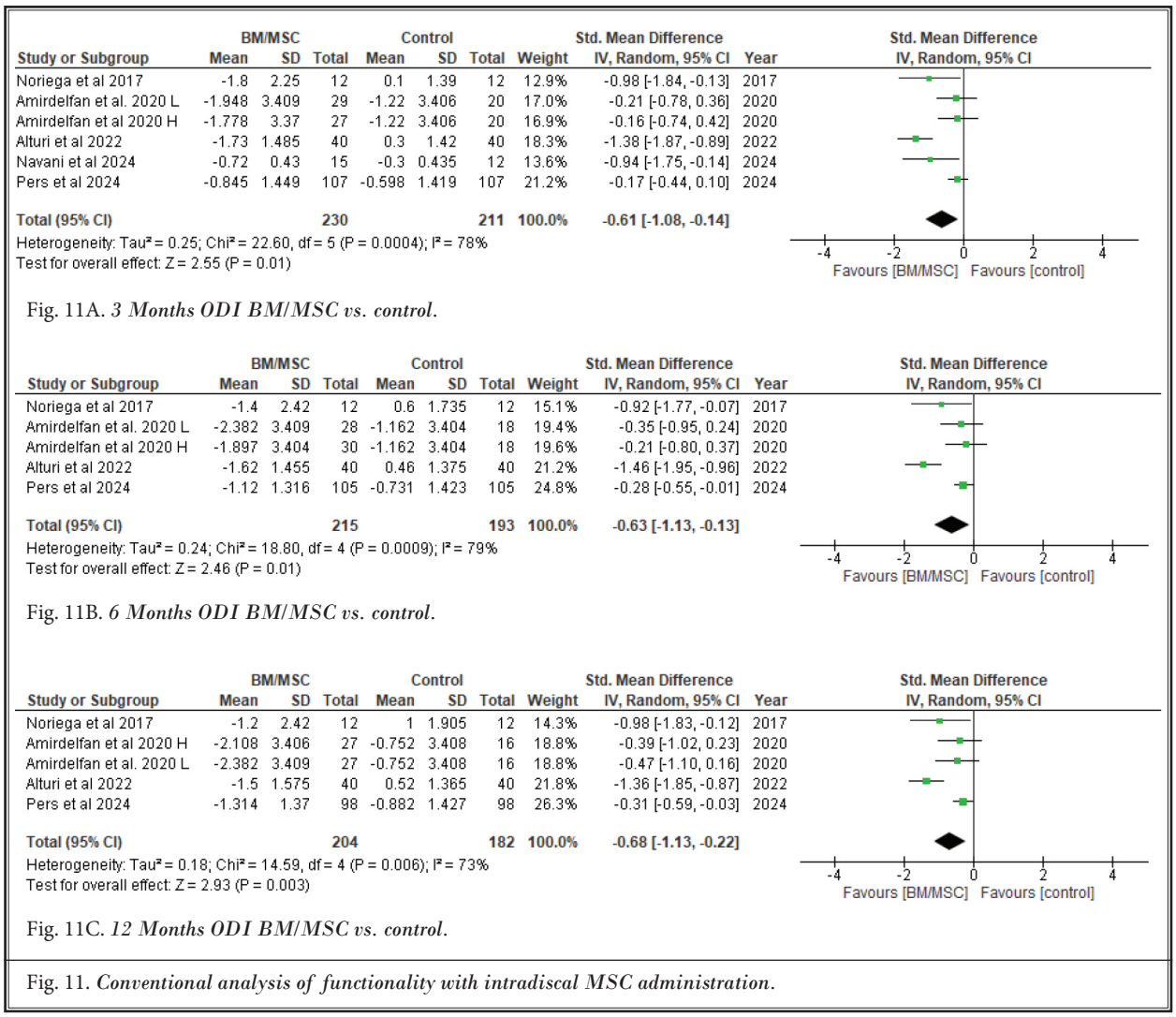


Fig. 11A. *3 Months ODI BM/MSC vs. control.*

Fig. 11B. *6 Months ODI BM/MSC vs. control.*

Fig. 11C. *12 Months ODI BM/MSC vs. control.*

Fig. 11. *Conventional analysis of functionality with intradiscal MSC administration.*

MRI, though findings were inconsistent. The overall GRADE score was very low due to heterogeneity and poor generalizability.

Soufi et al (416), without performing a meta-analysis, conducted a systematic review on stem cell therapy for degenerative disc disease and low back pain. They identified 11 clinical studies, including one RCT with 119 patients, and concluded there was no evidence to support the use of stem cell therapy in humans for these conditions.

Schneider et al (414), in a 2022 systematic review on intradiscal biologic treatments, including PRP and MSCs, included 12 studies and concluded that evidence quality was very low. One RCT evaluating PRP reported positive outcomes but had significant methodological flaws, while a single MSC trial showed negative results. Success rates for PRP injections were 54.8% and for MSCs 53.5% at 6 months, decreasing to 40.7% in a worst-case analysis. Functional improvement greater than 30% was achieved in 74.3% at 6 months, decreasing to 44.1% under worst-case assumptions. The authors concluded that limited observational data support intradiscal biologics for discogenic low back pain, but the evidence for MSCs and PRP was very low quality per GRADE criteria.

Kawabata et al (417) published a 2023 systematic review on advances in PRP for spinal diseases, highlighting promising regenerative potential from basic research and demonstrating safety and efficacy in clinical studies for degenerative disc disease.

Machado et al (10), in a 2023 systematic review on PRP for low back pain, included 13 RCTs and 27 non-randomized studies or case reports. Eleven of 13 RCTs showed favorable outcomes for pain and disability, one

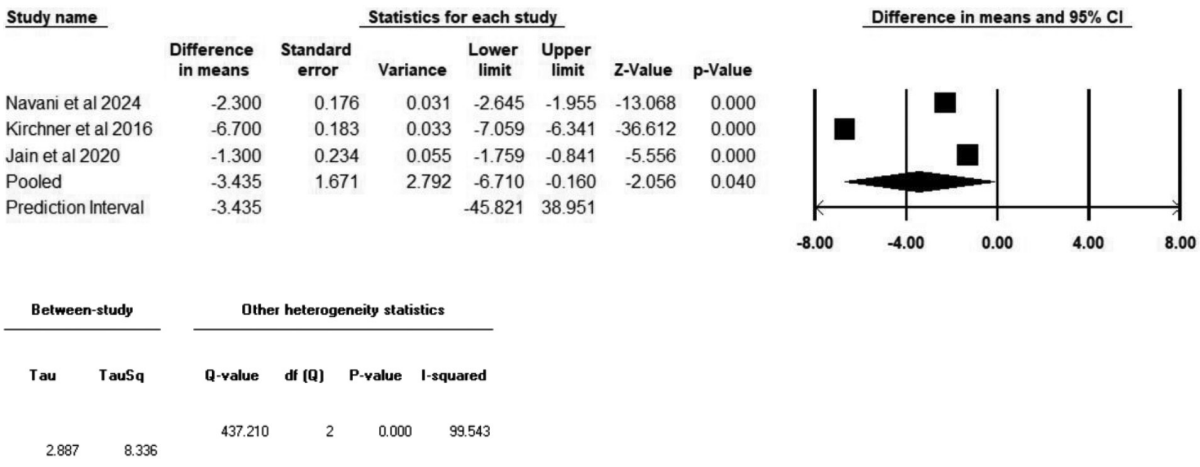


Fig. 12A. *Single-arm PRP meta-analysis on NRS at 3 months.*

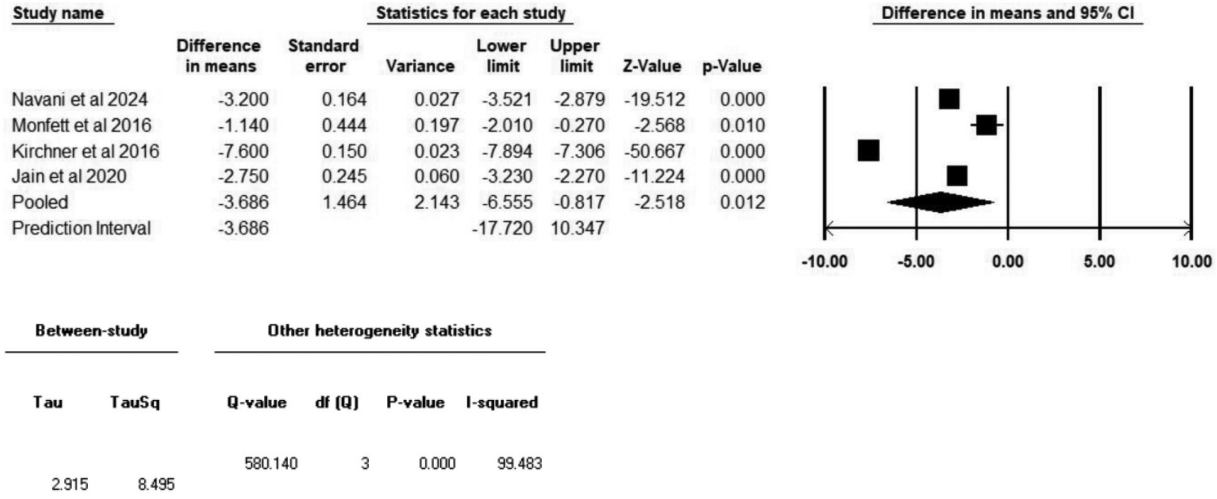


Fig. 12B. *Single-arm PRP meta-analysis on NRS at 6 months.*

Fig. 12. *Single-arm meta-analysis of pain relief with intradiscal administration of PRP.*

showed no superiority, and one was discontinued due to lack of therapeutic effect at 8 weeks. Injections included epidural, facet joint, and sacroiliac applications. Overall, PRP was found to be generally safe and effective, with a small number of adverse events. Evidence quality was rated as Level II, though the review lacked methodological and GRADE assessments.

Zhang et al (419), in 2024, evaluated PRP injection therapy for chronic low back pain through a network meta-analysis including 4 studies with 154 patients; only 2 studies focused on intradiscal injections. Corticosteroids provided better short-term pain improvement at 4 weeks, whereas PRP and radiofrequency ablation were similar. At 6 months, PRP demonstrated greater improvements in disability indices.

Peng et al (420), in a 2023 single-arm meta-analysis on intradiscal PRP for discogenic low back pain, included 6 trials (3 RCTs and 3 prospective single-arm trials), of which 2 studies (425,434) were part of this analysis. The meta-analysis showed 51.9% of patients achieved a 50% reduction in pain scores at 6 months, with a significant mean decrease of 1.42 points ($P = 0.0008$) and no significant adverse events reported.

Yum et al (95), in a 2024 review, emphasized the

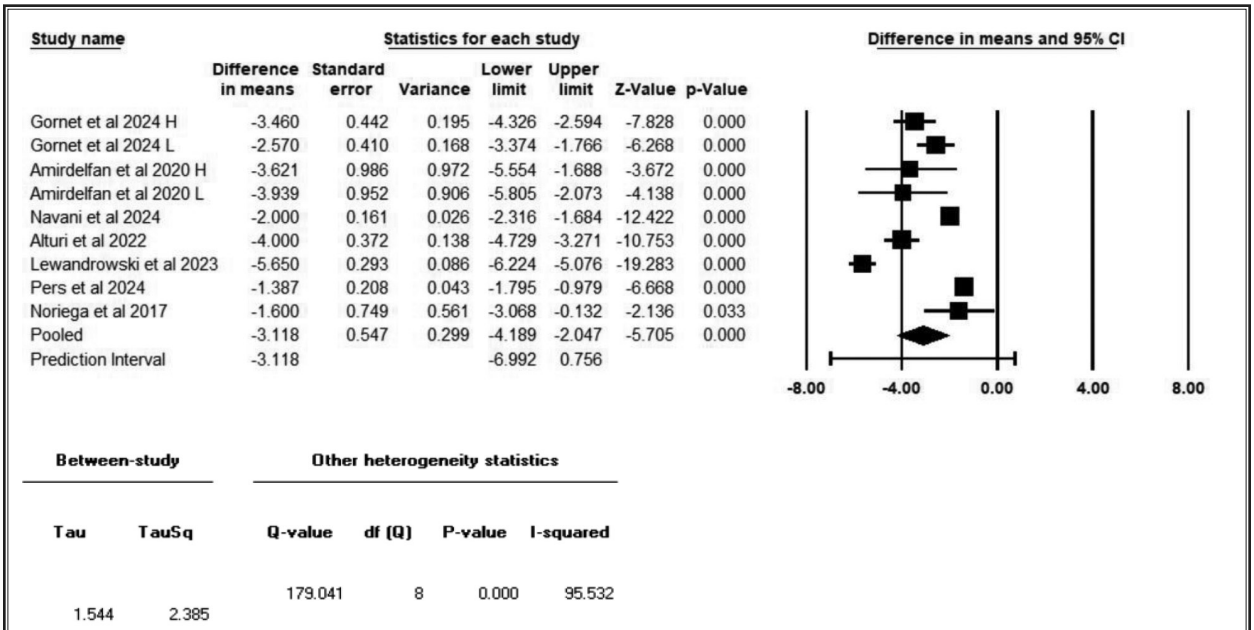


Fig. 13A. *Single-arm BM/MSC meta-analysis on NRS at 3 months.*

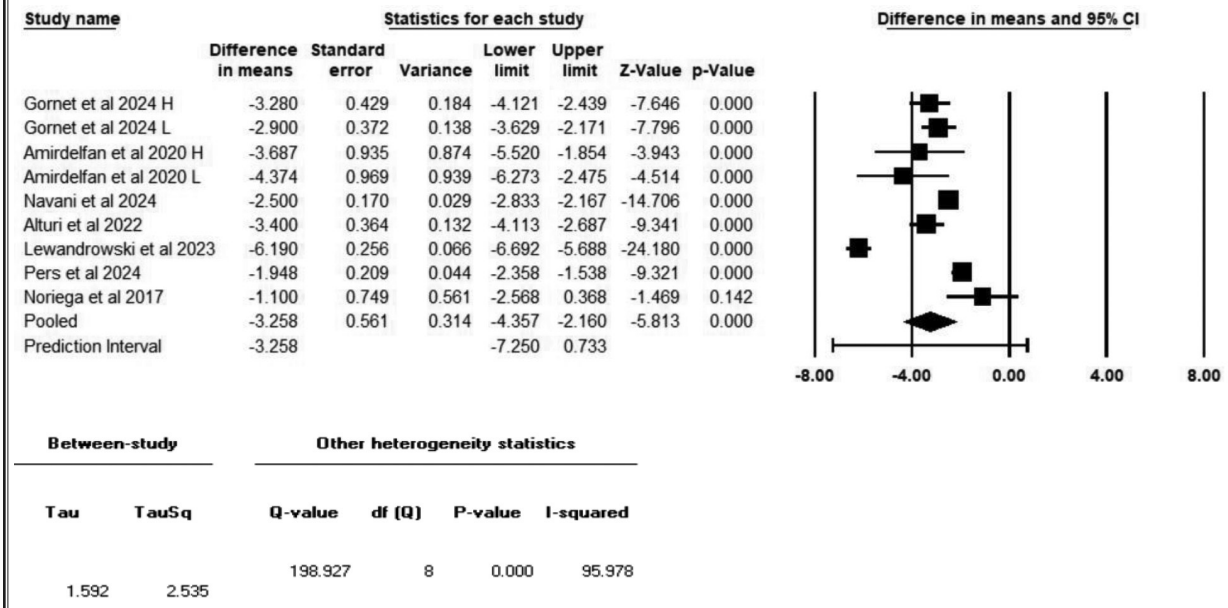


Fig. 13B. *Single-arm BM/MSC meta-analysis on NRS at 6 months.*

Fig. 13. *Single-arm BM/MSC meta-analysis of 3 and 6 months.*

need for full transparency in PRP preparation and injection protocols and recommended future double-blind RCTs to evaluate platelet concentration, dose, and timelines for expected clinical improvement. This publication was not a systematic review or meta-analysis.

Akeda et al (439), in a 2019 critical review, highlighted PRP's potential in stimulating cell proliferation and enhancing intervertebral cell metabolic activity in vitro and in vivo. Animal studies demonstrated that PRP injections improved disc height and matrix integrity, supporting PRP as a promising intradiscal therapy for degenerative disc disease.

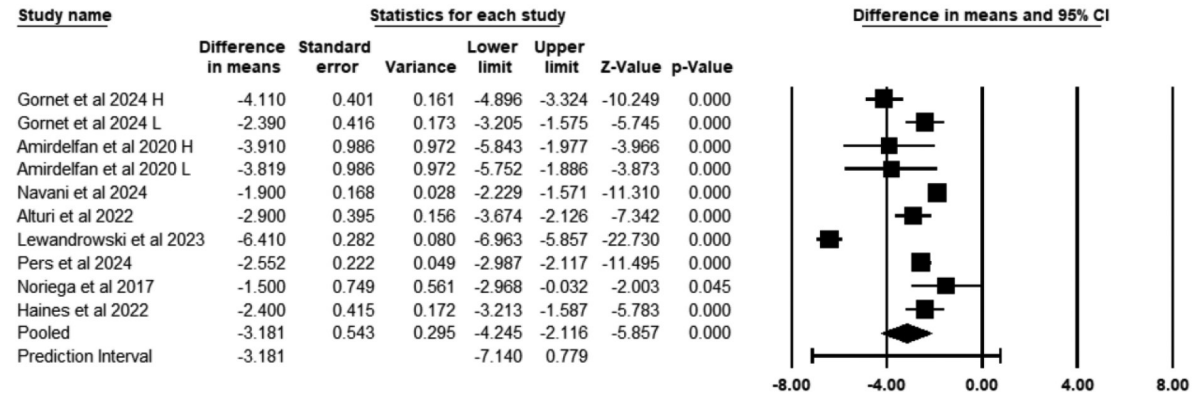


Fig. 14A. *Single-arm BM/MSC meta-analysis on NRS at 12 months.*

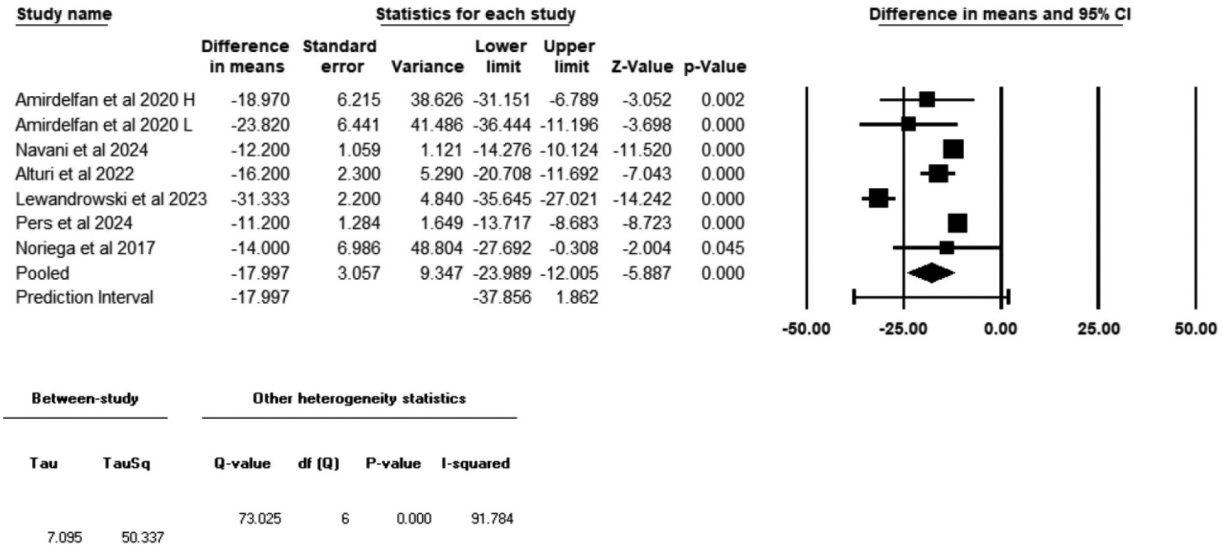


Fig. 14B. *Single-arm BM/MSC meta-analysis on NRS at 24 months.*

Fig. 14. *Single-arm analysis of long-term pain relief at 12 and 24 months with intradiscal PRP and MSC administration.*

Lorio et al (418), in 2024, provided a perspective on intradiscal therapies for lumbar discogenic pain, identifying MSCs, PRP, nucleus pulposus structural allograft, and other cell-based compositions as viable candidates. The review emphasized repairing, supplementing, and restoring damaged discs while preventing further degeneration, discussed FDA guidance on minimal manipulation and homologous use, and highlighted key evidence gaps and emerging technologies.

Bhujel et al (286), in 2022, reviewed MSC-derived exosomes in intervertebral disc regeneration, high-

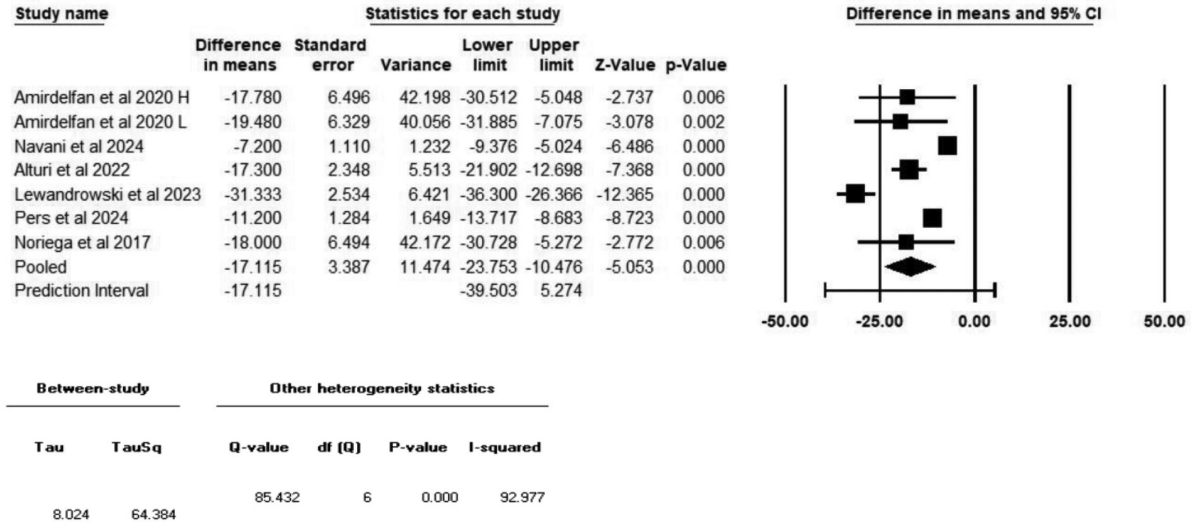


Fig. 15A. *Single-arm meta-analysis on functionality at 3 months.*

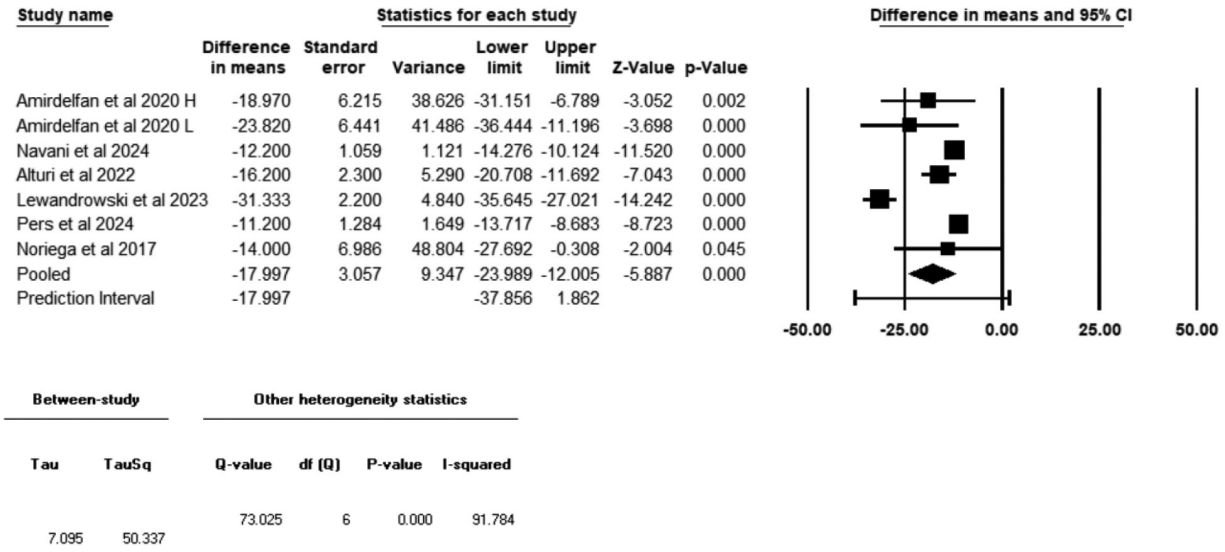


Fig. 15B. *Single-arm meta-analysis on functionality at 6 months.*

Fig. 15. *Single-arm meta-analysis on functionality at 3 and 6 months.*

lighting their paracrine-mediated effects, including promoting cell proliferation, tissue regeneration, modulating inflammation, and reducing apoptosis. Similarly, Akeda et al (439) confirmed PRP's potential to stimulate intervertebral cell activity and restore structural disc changes.

Overall, multiple systematic reviews and meta-analyses indicate that intradiscal MSCs and PRP have potential benefits for discogenic low back pain. Existing evidence from RCTs and observational studies suggests effectiveness in pain reduction and functional improvement, but additional high-quality studies are required to further clarify their role in mediating and modulating treatment outcomes.

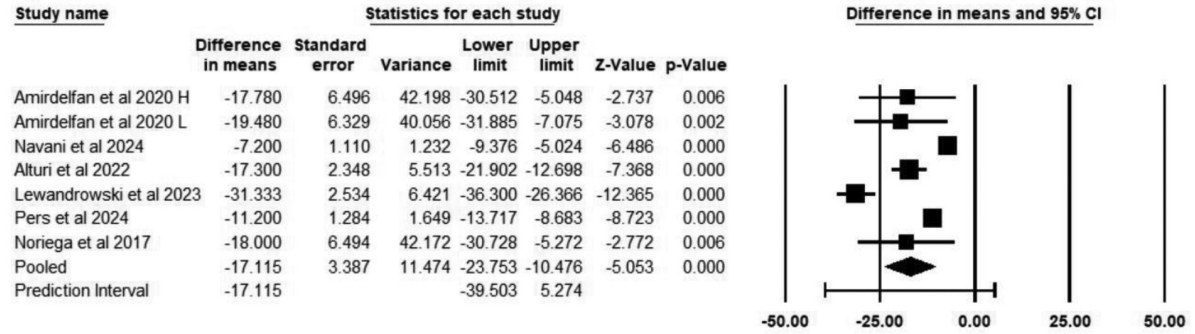


Fig. 16A. *Single-arm meta-analysis on functionality at 12 months.*

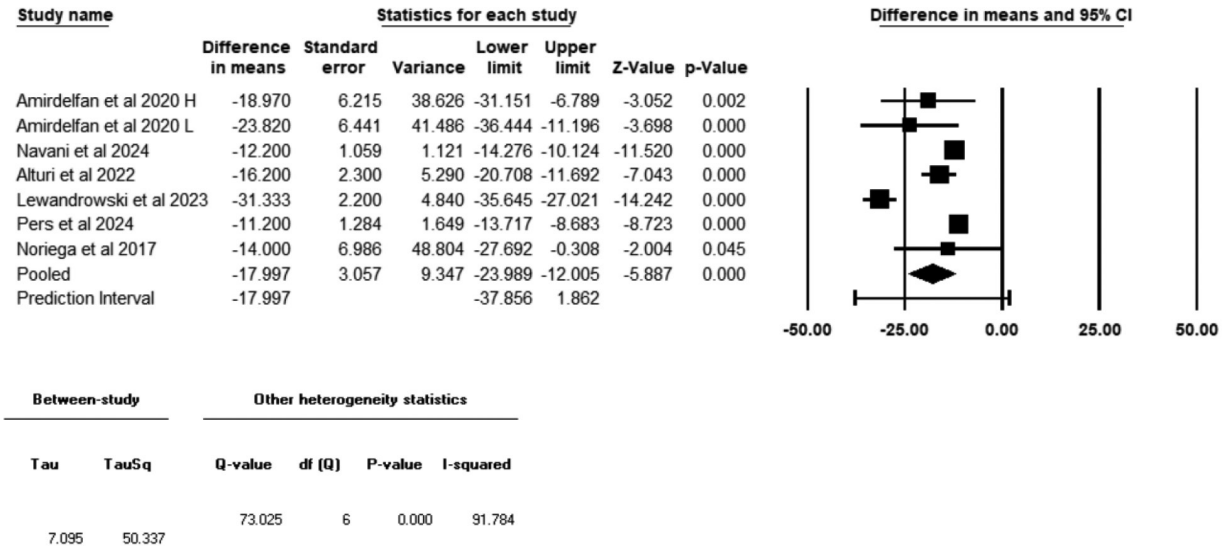


Fig. 16B. *Single-arm meta-analysis on functionality at 24 months.*

Fig. 16. *Single-arm analysis of long-term improvement in functionality at 12 and 24 months with intradiscal MSC administration.*

7.2 Epidural Injections

Key Question 5. The evidence of effectiveness for the use of epidural injections of PRP and derivatives and consensus-based clinical recommendations.

Since intervertebral discs are the body's largest avascular structures with limited regenerative capacity (60), they depend on nutrient diffusion from capillaries at the vertebral body margins through the cartilaginous endplates. This nutritional limitation has prompted therapeutic strategies aimed at enhancing disc nutrition and regeneration. Regenerative approaches, including PRP and MSCs, are being investigated for their potential to promote disc healing (440-449). PRP contains multiple cytokines and growth factors, such as

Table 11. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
PLATELET-RICH PLASMA									
Tuakli-Wosornu et al, 2016 (425)	RA, PC, DB	Low	NS	NS	NS	Low	47 PRP = 29 Comparator = 18	Positive trial Intradiscal injections of PRP x 1 showed significant improvement at 8-week follow-up with maintained improvement compared to controls at 1-year follow-up.	Moderate
Navani et al, 2024 (11)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	43 Placebo = 12 PRP = 15 BMC = 16	Positive trial Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC	Moderate
Goyal et al, 2022 (427)	RA, AC	Low/ Moderate	NS	NS	NS	Low	48 PRP = 24 PIRF = 24	Negative trial for PRP The response to intradiscal injection of PRP showed poor response with 4 of 26 patients responding at 3 months and 11 of 26 patients responding at 6 months	Low
Akeda et al, 2022 (428)	RA, AC, DB	Low	NS	NS	NS	Low	16 PRPr = 8 Comparator = 8	Positive PRP trial Significant improvement at 60 weeks in PRPr group compared to baseline data; however, even though it was different, it did not reach statistical significance in comparison with the steroid group	Moderate
MESENCHYMAL STEM CELLS									
Pers et al, 2024 (429)	RA, PC, DB	Low	NS	NS	NS	Low	114 BM-MSC = 58 Sham placebo group = 56	Negative trial A large multicenter, RA, PC, trial in degenerative disc disease using a single intradiscal injection of allogenic MSCs, showed no clinical and imaging benefits at 12-month follow-up There were only non-significant improvements in various parameters including disc fluid content, VAS, ODI, with BM-MSC scoring better	Low

Table 11 cont. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
Navani et al, 2024 (11)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	43 Placebo = 12 PRP = 15 BMC = 16	Positive trial Comparative analysis of intradiscal PRP and BMC compared to intramuscular injection of muscle saline injection into the muscle showed significant improvement in biologic treatment groups There was no difference in PRP or BMC	Moderate
Noriega et al, 2017 (426)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	24 MSC = 12 Comparator = 12	Positive trial 40% of patients with perfect results 28% improvement in all patients Degeneration improved in MSC treated patients and worsened in the controls. Feasibility and safety were confirmed in this preliminary trial	Low
Amirdelfan et al, 2021 (424)	RA, PC, DB	Low/ Moderate	NS	NS	NS	Low	100 Allogeneic expanded STRO-3+ MPCs from iliac crest, 2cc per injection	Positive trial Positive results with safety and efficacy in a randomized, multi-site trial with multiple variables; however, there were no significant radiographic improvements in any of the groups	Moderate
Gornet et al, 2024 (430)	RA, PC, DB, AC	Low	NS	NS	NS	Low	60 Intradiscal biologics Low dose cells (n = 20) High dose cells (n = 20) Vehicle alone (n = 10) Placebo n = 10	Positive allogeneic disc progenitor cells trial Significant effectiveness of high-dose allogeneic disc progenitor cells with clinically meaningful improvement in back pain and disc volume at one-year and 2 years.	Moderate

AC = active controlled; BMC = bone marrow concentrate; BM-MSC = bone marrow mesenchymal stromal cell; DB = double-blind; MSC = mesenchymal stem cells; NS = Not serious; PC = placebo controlled; PRP = platelet-rich plasma; PIRF = percutaneous intradiscal radiofrequency; PRPr = platelet-rich plasma releasate; RA = randomized; STRO-3 = stromal precursor antigen-3

IL-1RA, TGF-β1, platelet-derived growth factor (PDGF), and insulin-like growth factor-1 (IGF-1) (440). Its autologous and antimicrobial properties provide a favorable safety profile, reducing the risk of immunogenic reactions, adverse effects, and infections (441).

Although some disc-related pain and radiculopathy resolve spontaneously, many cases progress to chronic pain requiring more intensive interventions. Management strategies range from conservative therapies, including physical therapy and medications, to interventional procedures and surgeries such as spinal fusion or disc replacement (38,98,99,101,102,105). Interventional techniques, including epidural injections and regenerative therapies, are increasingly employed for chronic spinal pain (10,17,20,21,38,39,42,85,95,98,99,101,102,105,107,110,111,283,413, 415-417,419, 439,450-453).

Disc degeneration is a major contributor to discogenic pain, primarily through inflammation-induced nociceptive innervation within the disc (11,60). The intervertebral disc architecture, consisting of the nucleus pulposus, annulus fibrosus, and cartilaginous endplates, supports structural integrity and shock absorption. Degeneration impairs these functions, resulting in lumbar spine instability (454,455). Conventional treatments fail to halt or reverse the degenerative process (10,17,18,111,284,413,415-417,419,439). Key mechanisms implicated in disc degeneration include loss of stem and progenitor cells, extracellular matrix degradation, inflammation, aberrant sensory innervation, neovascularization, and disrupted signaling pathways. Regenerative interventions using MSCs and PRP are emerging as potential solutions (10,17,18,95,107,110,111,280-283,410-420,439,453,456,457).

Yum et al (95), in a 2024 review, highlighted critical gaps in PRP application for lumbar spine conditions. They emphasized the need for complete transparency in PRP preparation and injection protocols in clinical studies and recommended future double-blind, randomized trials to assess platelet concentration, dosage, and treatment timelines. This publication was not a systematic review or meta-analysis.

Sanapati et al (17) reviewed 9 publications on epidural cell-based therapies for lumbar discogenic low back pain, including one RCT and 3 single-study reports. Due to small sample sizes and other limitations, these studies were excluded from the present analysis. A single-arm analysis of 6 studies (including one RCT, n = 71) demonstrated a significant reduction in pain scores at 12 months by 36.943 points (95% CI: -49.855 to -24.030, $P < 0.001$; $I^2 = 86\%$) and a 26.342-point improvement in disability scores (95% CI: -32.359 to -20.325, $P < 0.001$; $I^2 = 55\%$). The authors concluded that MSCs and PRP may be effective for discogenic low back pain, radicular pain, facet joint pain, and sacroiliac joint pain, although the level of evidence varied.

Muthu et al (458) conducted a meta-analysis of 5 RCTs involving 310 patients (PRP: 153; Steroids: 157) to evaluate the safety and efficacy of epidural PRP versus steroid injections for radiculopathy due to lumbar disc disease. Outcomes were assessed at multiple timepoints up to 48 weeks. PRP provided comparable results for pain relief, functional status, and overall health without increased adverse events. The authors concluded that epidural PRP offers similar benefits and safety to steroid injections.

Manchikanti et al (20) performed a systematic review and meta-analysis following PRISMA guidelines (421), including 9 RCTs (456,457,459-465) on epidural biologics for chronic spinal pain. No additional studies were identified. Evidence quality was rated as fair (Level III), with moderate effect size and recommendation strength based on qualitative synthesis and GRADE methodology. Study characteristics are shown in Table 12. Methodologic quality and risk of bias were assessed using standardized metrics (Appendix Tables 1 and 2). Conventional meta-analysis results are presented in Figs. 17 and 18, and all RCTs were included in certainty assessment using GRADE criteria (Table 13).

For qualitative analysis, 7 RCTs used PRP (456,457,460-464) and 2 used autologous conditioned serum (459,465), with 8 positive studies (456,457,459,460,462-465) and one neutral trial (461). All studies were randomized, with no observational studies included. Meta-analysis showed slight favorability for PRP in pain relief at 3 and 6-months, with no differences in functional status at these time points. Evidence quality was rated fair (Level III), with low to moderate certainty and moderate recommendation strength based on qualitative and quantitative assessment.

7.3 Facet Joint Injections

Key Question 6. The evidence of effectiveness for using intra-articular facet joint injections of PRP and consensus-based clinical recommendations.

Current literature identifies multiple potential sources of spinal and extremity pain, established

Table 12. *Study characteristics of randomized controlled trials assessing epidural injections of PRP and derivatives.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Gupta et al, 2024 (456) RCT, AC Quality Scores: Cochrane = 13/13 IPM-QRB = 32/48	46 patients Lumbar intervertebral disc prolapse with radiculopathy Biologic Used: PRP Epidural injection of PRP n = 23 Epidural injection utilizing Corticosteroids n = 23	n = 23 Epidural injection of PRP 3 mL. PRP was prepared from 30 mL of whole blood, resulting in 3-5 mL of PRP Multiple injections of PRP were provided	n = 23 Epidural injection 0.5 mL of 0.5% bupivacaine and 1 mL of 1 mL (40 mg) of triamcinolone Multiple injections of steroids were provided in steroid group, as well as PRP group	75% pain relief as success criteria compared with pre-procedural pain VAS ODI SF-12 scores 1 week, 3 weeks, 6 weeks, 6 months, 1 year	At the 6-month follow-up, 39% of the patients in the steroid group and 56% of the patients in PRP group continued to demonstrate improvement. At one-year follow-up, 26% of the patients in the steroid group and 30% of the patients in PRP group demonstrated significant improvement in all outcome measures. In the PRP group, 7 patients received repeat lumbar transforaminal injections and 9 underwent surgery. Further, in the PRP group, 7 patients received repeat injection of steroids. In the steroid group, 9 patients received more transforaminal injections, and 8 patients underwent surgery at one-year follow-up.	Randomized controlled trial	Active control trial Relatively small sample size 3-5 mL of PRP obtained from 30 mL of whole blood which is considered as inadequate The data was not clear enough at 3 months	Positive PRP trial Significant improvement in pain relief (> 75%) and improvement in function at 6 months in PRP group compared to corticosteroid group
Jayasoorya et al, 2024 (462) RCT, AC Quality Scores: Cochrane = 9/13 IPM-QRB = 23/48	64 patients Low back pain of discogenic origin Biologic Used: PRP Epidural injection of PRP n = 32 Epidural injection utilizing Corticosteroids n = 32	n = 32 Epidural injection of PRP 3 mL. PRP was prepared from 20 mL of whole blood, resulting in 2-4 mL of PRP	n = 32 Epidural injection of methylprednisolone 1.5 mL, 1.5 mL of 2% lidocaine, and 0.5 mL of sodium chloride solution	VAS MODQ SLRT 3 months	In terms of VAS ratings, MODQ scores, and SLRT, study subjects who received autologous PRP injections via lumbar epidural demonstrated a greater improvement in the symptoms with pain relief, disability and SLRT At 3 months, the methylprednisolone group with a baseline VAS of 7.06 ± 0.098 reduced to 5.2 ± 0.65, whereas in the PRP group baseline VAS was 7.21 ± 1.31, which reduced to 3.26 ± 0.79 with statistically significant difference ($P = < 0.05$) ODI scores showed that number of patients suffering with severe disability decreased from 27 to 19 after 3 months in corticosteroid group compared to from 23 to 9 after 3 months in the PRP group SLRT test scores also improved	Randomized controlled trial	Active control trial Small sample size Poor description of technique and patient management and blinding 2-4 mL of PRP was obtained from 20 mL of whole blood which is considered as inadequate	Positive PRP trial Significant improvement in pain relief at 3 months in PRP group compared to corticosteroid group There were also clinically significant differences with ODI questionnaire and SLRT scores

Table 12 cont. *Study characteristics of randomized controlled trials assessing epidural injections of PRP and derivatives.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Wongjarupong et al, 2023 (464) RCT, AC Quality Scores: Cochrane = 13/13 IPM-QRB = 32/48	30 patients Lumbar disc herniation Biologic Used: PRP PRP Group n = 15 Triamcinolone Group n = 15	n = 15 Transforaminal epidural injection under fluoroscopic guidance with injection of 2 mL of PRP was injected PRP was prepared from 26 mL of whole blood with resultant PRP of 3 mL	n = 15 Transforaminal epidural steroid injection under fluoroscopic guidance with a total of 2 mL of 1% lidocaine with 40 mg of triamcinolone	Leg VAS Back VAS ODI 2, 6, 12, and 24 week follow-up	Leg VAS was significantly reduced ($P = 0.002$) from baseline of 65.27 ± 15.32 for PRP to 15.33 ± 9.9, compared to 59.67 ± 19.68 to 30 ± 7.45 with triamcinolone. ODI reduced for PRP from 44.73 ± 10.71 to 15.07 ± 7.79, compared to for triamcinolone of baseline 43.13 ± 10.81 to 21.3 ± 5.21. This was statistically not significant; however, clinically significant with higher mean difference between groups and also >50% reduction from baseline in both groups. Back VAS for PRP reduced from baseline of 64.27 to 17.53 to at 24 weeks 17.8 ± 11.33, compared to baseline of 73 ± 13.86 to 28.5 ± 10.29 for triamcinolone. There was no statistically significant difference; however, the differences were clinically relevant in both groups, specifically in PRP with a reduction of over 60%.	Randomized controlled trial	Active control trial Small number of patients PRP was suboptimal with 26 mL of whole blood with resultant PRP of 3 mL	Positive trial of PRP compared to epidural steroids The results showed significant improvement with leg VAS. Results also showed clinically relevant reductions in Back VAS and ODI, even though it did not reach statistically significant difference
Godek et al, 2023 (465) RCT, AC Quality Scores: Cochrane = 11/13 IPM-QRB = 23/48	100 patients Lumbar degenerative disc disease Biologic Used: ACS (Orthokine) Group A: Epidural interlaminar approach with ultrasound-guided injections utilizing ACS (Orthokine) n = 50 Group B: Perineural injection with ultrasound guided injections utilizing ACS (Orthokine) n = 50	n = 50 Group A: Epidural with interlaminar approach, 2 ultrasound-guided injections as control intervention each containing 2 doses of ACS (Orthokine), 8 mL	n = 50 Group B: Perineural (periarticular) approach – 2 ultrasound guided injections as experimental interventions at 7-day intervals with 2 doses of ACS (Orthokine), 8 mL	NRS ODI RMDQ EQ-5D-5L VAS LSS 4 weeks, 12 weeks, 24 weeks	Both perineural and interlaminar epidural injections showed similar results at 24-week follow-up with significant improvement in ODI scores, RMDQ scores, EQ-5D-5L mobility scores, EQ-5D-5L self-care scores, and EQ-5D-5L usual activities There was no significant difference among the groups. The effect size of perineural group was superior with a statistically significant superiority in favor of the perineural group for EQ-5D-5L mobility ($P = 0.0432$) and index ($P = 0.0359$) at week 12	Randomized controlled trial	Active control trial A comparison of 2 techniques High volume of ACS (Orthokine) 2 injections at 7-day intervals for both interlaminar and transforaminal epidural injections The needle position was not confirmed under fluoroscopy Same volumes were considered very high for transforaminal group	Positive trial of ACS (Orthokine) in lumbar degenerative disc disease There was no significant difference with either approach. This was a technical comparison. There were 2 injections 7 days apart The volumes of injections were similar for interlaminar and transforaminal group which is considered as very high

Table 12 cont. *Study characteristics of randomized controlled trials assessing epidural injections of PRP and derivatives.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Singh et al, 2023 (463) RCT, AC Quality Scores: Cochrane = 10/13 IPM-QRB = 27/48	45 patients Prolapsed lumbar intervertebral disc Biologic Used: PRP Group 1: PRP n = 23 Group 2: Steroid with local anesthetic n = 22	n = 23 Under fluoroscopic guidance, peri-discal injection of PRP, 3 mL, was injected	n = 22 Peri-discal injection of steroid (triamcinolone 40 mg, 1 mL) with local anesthetic (bupivacaine 0.25%, 2 mL)	NRS GPE Up to 6 months	Intervention Group: 3 mL of PRP was derived from 30 mL of whole blood. Concentration of platelets in the prepared PRP was ensured to be at least 3 to 5 times higher than that in whole blood (i.e., 450,000 to 17,500,000 per µl range At initial follow-up of one-month, epidural steroids were superior. 6-month follow-up: PRP group showed reduction of NRS from 6.91 ± 0.94 to 1.43 ± 0.75 compared to steroid group where from baseline of 7.38 ± 1.16 to 5.43 ± 0.75 with statistically significant difference ($P < 0.001$) GPE scores also showed significant difference of ($P < 0.001$).	Randomized controlled trial Amount of whole blood extracted was 30 mL, even though this is lower than recommended 60 mL, but better than other studies using only 20 mL	Small number of patients Active control trial 30 mL of whole blood rather than 60 mL extracted	Positive trial of PRP compared to epidural steroids At 6-month follow-up superior results were demonstrated with PRP with pain rating, as well as GPE scores.
Saraf et al, 2023 (457) P, RCT, DB Quality Scores: Cochrane = 12/13 IPM-QRB = 26/48	60 patients Discogenic lumbar radiculopathy Biologic Used: PRP Single transforaminal injection of PRP n = 29 Single transforaminal injection of steroid n = 31	n = 29 Single transforaminal injection of 3 mL of autologous PRP	n = 31 Single transforaminal injection of steroid with 2 mL of methylprednisolone acetate (40 mg/mL0 with 1 mL 1% lignocaine	VAS MODI SLRT 1 month, 3 months, and 6 months	There was significant statistical improvement of VAS and MODI in both groups at follow-up ($P < 0.05$) In PRP group, minimal clinically important change (> 2 cm difference of mean for VAS and > 10-point change in MODI) for both outcome scores was achieved at all follow-up intervals of 3 and 6 months In the steroid group, improvement was seen only at 3 months for both VAS and MODI In comparison of both groups, better results were seen with PRP at 6 months ($P < 0.001$ for both VAS and MODI), however, there was no significant difference at 3 months SLRT was negative in 90% in PRP group and 62% in steroid group at 6 months.	Randomized controlled trial	Active control trial Relatively small sample	Positive PRP trial PRP showed significantly better outcomes at 3 and 6 months in reference to pain, function, and SLRT

Table 12 cont. *Study characteristics of randomized controlled trials assessing epidural injections of PRP and derivatives.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Xu et al, 2021 (461) RCT, AC Quality Scores: Cochrane = 11/13 IPM-QRB = 33/48	124 patients Lumbar disc herniation Biologic Used: PRP Ultrasound guided transforaminal injection n = 61 Ultrasound guided epidural steroid injection n = 63	n = 61 Transforaminal epidural under ultrasound guidance PRP was prepared from 80 mL of blood with 4 mL of PRP. 3 mL of autologous PRP injection	n = 63 Epidural injection of local anesthetic and steroids with 2 mL of betamethasone + 0.5 mL of 0.9% sterile saline + 0.5 mL of 2% lidocaine	VAS PPT ODI Physical function SF-36 Latency of F-wave 1 week, 1 month, 3 months, 6 months, 12 months	Similar results for both epidural injection and PRP VAS improved from baseline of 6 to 2.0 at end of one-year in PRP group as well as steroid group ODI improved from baseline of 35 to 19 in PRP group and to 20 in ODI group There was significant improvement in both groups compared to baseline	A randomized, active controlled trial	Procedure was performed with high volume injection of PRP and steroid solutions with spread may have extended to multiple segments Procedure was performed under ultrasound guidance without fluoroscopic confirmation.	Neutral trial of PRP and steroid injections Both groups showed significant improvements in VAS and ODI, as well as other parameters compared to baseline; however, there was no difference between the groups
Ruiz-Lopez & Tsai, 2020 (460) RCT, AC Quality Scores: Cochrane = 13/13 IPM-QRB = 30/48	50 patients Complex chronic degenerative spinal pain Biologic Used: LR-PRP Caudal epidural injections of LR-PRP or corticosteroid administered under fluoroscopic guidance	LR-PRP n = 25 Caudal epidural injection under fluoroscopic guidance with injection of 20 mL of LR-PRP mixture with 16.5 mL of LR-PRP and 3.5 mL of non-ionic iohexol contrast medium. LR-PRP was prepared from autologous blood of 60 mL with addition of 5 mL of acid citrate dextrose with final extraction of 16.5 mL of LR-PRP.	Caudal epidural steroid injection with local anesthetic n = 25 Caudal epidural under fluoroscopic guidance with a total of 20 mL corticosteroid mixture (60 mg triamcinolone with local anesthetic and 3.5 mL of contrast medium)	VAS SF-36 1, 3, and 6 months	Significantly lower VAS scores were reported in patients who received LR-PRP injections. In reference to SF-36 measurements only patients receiving LR-PRP had a significant improvement in domains which included physical functioning, role-physical, general health, and physical component summary. Caudal epidural administration of triamcinolone acetonide or LR-PRP significantly improved the levels of lumbar pain up to 6 months after treatment. Compared with the LR-PRP group, significantly lower VAS scores were shown in the corticosteroid group at one-month.	Randomized controlled trial	Active control trial Small sample size Preparation of PRP was inadequate compared to the standardization protocols with 60 mL of blood deriving a total of 16.5 mL of PRP which may explain the suboptimal results.	Positive Positive trial of PRP of caudal epidural compared to corticosteroids

Table 12 cont. *Study characteristics of randomized controlled trials assessing epidural injections of PRP and derivatives.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Becker et al, 2007 (459) RCT, AC Quality Scores: Cochrane = 11/13 IPM-QRB = 32/48	84 patients Lumbar radicular pain Biologic Used: ACS (Orthokine) Epidural perineural injection with ACS (Orthokine) n = 32 Epidural perineural triamcinolone 10 mg n = 25 Epidural perineural triamcinolone 5 mg n = 27	Transforaminal or perineural injection of ACS (Orthokine) once per week for 3 consecutive weeks. First Group (n = 32): 1 mL of ACS (Orthokine) was injected reaching the nerve root through an oblique interlaminar approach with 29-gauge spinal needle	Second Group (n = 25): Triamcinolone 10 mg with 1 mL of local anesthetic approaching the nerve root through oblique interlaminar approach with a 29-gauge spinal needle Third Group (n = 27): Triamcinolone 5 mg with 1 mL of local anesthetic approaching the nerve root through oblique interlaminar approach with a 29-gauge spinal needle	VAS ODI 6 weeks, 10 weeks, and 22 weeks	At week 12 patients receiving ACS (Orthokine) showed a consistent pattern of superiority over both triamcinolone groups with regard to the primary outcome measure of VAS. Statistically significant difference was observed at 22 weeks in direct comparison to the treatment of 5 mg group. There was no statistically significant difference between all groups with respect to ODI. Pairwise comparisons of treatment groups and VAS at end of observation showed with a mean difference of -13.5 with 5 mg triamcinolone and -9.3 with 10 mg triamcinolone	Randomized controlled trial with comparison of ACS (Orthokine) and triamcinolone in 2 separate doses The most pronounced pairwise difference was found between ACS and triamcinolone 5 mg, mean 13.5 in favor of ACS (Orthokine)	Active control trial. There was no significant difference with ODI. Multiple injections	Positive trial of ACS (Orthokine) compared to triamcinolone ACS (Orthokine) was superior to triamcinolone at 26 weeks The results of epidurals are as expected to deteriorate after several weeks after 22 weeks.

AC = active controlled; ACS = autologous conditioned serum; DB = double-blind; EQ-5D-5L = EuroQol 5 Dimension; GPE = Global Perceived Effect; IPM-QRB = Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment; LSS = level sum score; LR-PRP = leucocyte-rich platelet-rich plasma; MODQ = Modified Oswestry Disability Questionnaire; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; P = prospective; PPT = pressure pain thresholds; PRP = platelet-rich plasma; RCT = randomized controlled trial; RMDQ = Roland Morris Disability Questionnaire; SF-12 = 12-Item Short Form Health Survey; SLRT = straight leg raising test; SF-36 = 36-item Short Form Health Survey; VAS = Visual Analog Scale

through controlled diagnostic blocks, including the intervertebral discs, facet joints, nerve root dura, and sacroiliac joints (41). For axial spinal pain of facet joint origin, 3 primary interventional modalities are commonly employed: therapeutic facet joint nerve blocks, radiofrequency neurotomy of lumbar medial branch nerves, and intra-articular injections (41). Despite their widespread use, the economic and societal burden of chronic spinal pain continues to rise due to the increasing application of diverse treatment modalities (2,6,17,38,41,100,102-105,110,219,466-469). Among these, regenerative medicine approaches, particularly PRP and stem cell injections, have gained attention for use in various spinal structures, including facet joints (6,17,95,108-110,470-472).

Several systematic reviews have evaluated regenerative therapies for chronic spinal pain. Ambrosio et al (470) conducted a systematic review of minimally invasive interventional treatments for chronic low back pain caused by lumbar facet joint syndrome, including intraarticular PRP. They found that intraarticular PRP resulted in long-term improvements in pain, disability, and patient satisfaction compared to corticosteroid injections. One

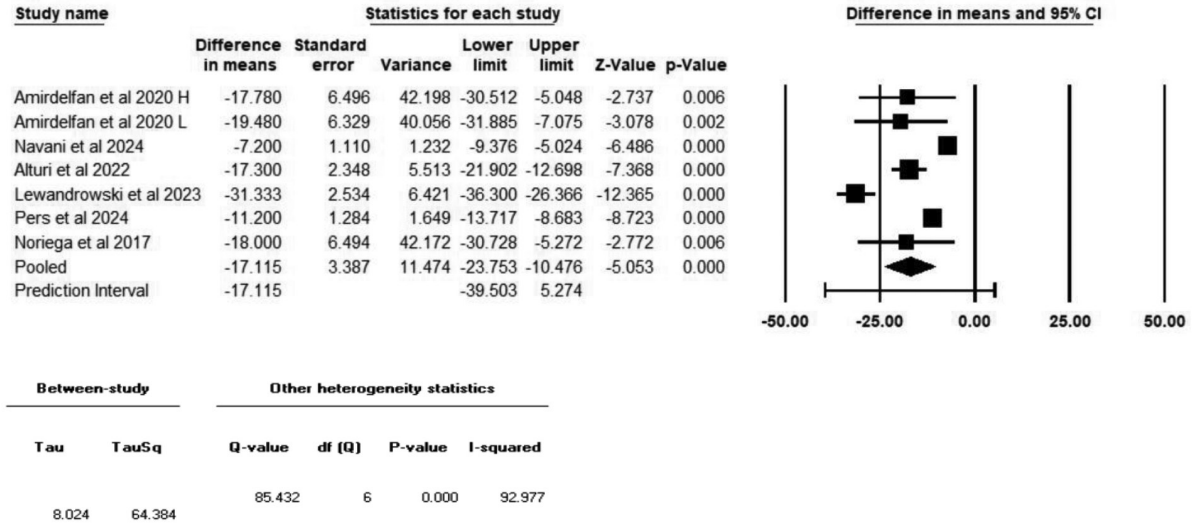


Fig. 17A. *Pain relief at 3 months with epidural injection of PRP compared to steroids.*

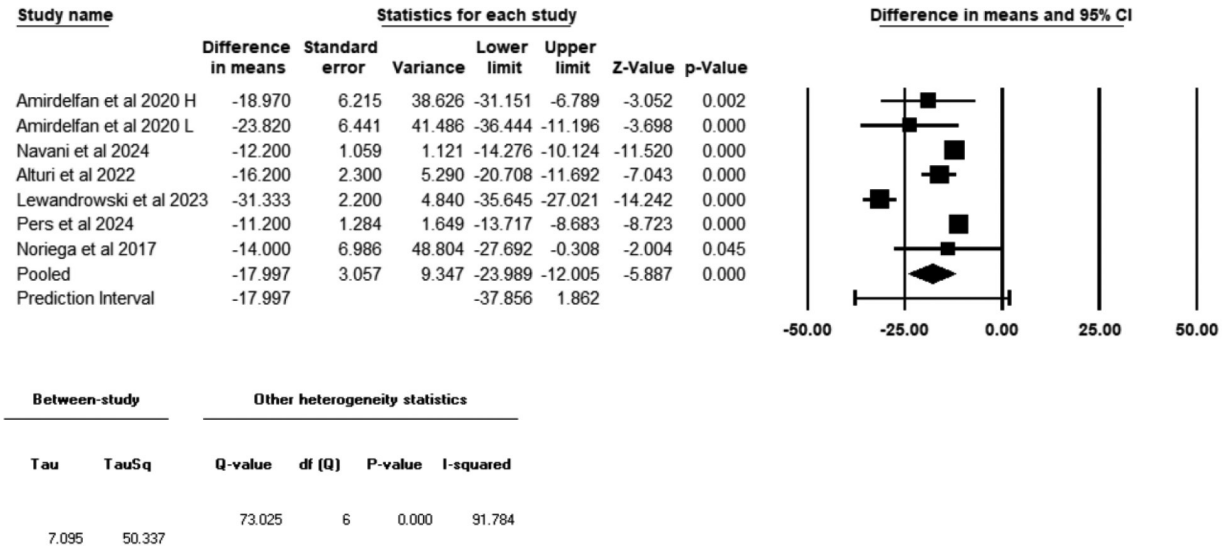


Fig. 17B. *Pain relief at 6 months with epidural injection of PRP compared to steroids.*

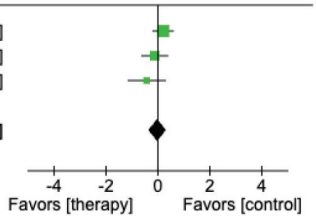
Fig. 17. *Analysis of pain relief with epidural injection of PRP compared to steroids.*

RCT by Wu et al (473), included in the review, provided supporting evidence for the efficacy of intraarticular PRP.

Sanapati et al (17) performed a comprehensive literature review on lumbar facet intra-articular injections, incorporating a single-arm meta-analysis. Their review included 3 studies evaluating PRP in lumbar facet joint injections (432,473,474), concluding that the qualitative evidence for PRP was limited, rated as Level IV.

Machado et al (10), in a systematic review of PRP for low back pain, identified PRP as a promising alternative for patients with lumbar facet syndrome. They reported that intra-articular PRP injections demonstrated both safety and effectiveness, with no complications compared to local anesthetics or corticosteroids.

Zhang et al (419) conducted a network meta-analysis of RCTs comparing PRP injections to various control groups. Their findings indicated that PRP was

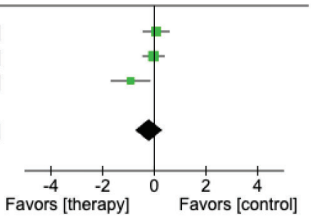


Study or Subgroup	Therapy Mean	Therapy SD	Therapy Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, Random, 95% CI
Godek et al	11.83	7.26	46	10.31	7.72	49	47.0%	0.20 [-0.20 , 0.60]
Saraf et al	36.2	9.7	29	37.5	10.3	31	34.0%	-0.13 [-0.64 , 0.38]
Wongjarupong et al	18.07	8.06	15	21.64	7.92	15	19.0%	-0.43 [-1.16 , 0.29]
Total (Wald[a])			**90**			**95**	**100.0%**	**-0.03 [-0.37 , 0.31]**

Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.02; Chi² = 2.58, df = 2 (P = 0.28); I² = 23%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Fig. 18A. *Change in function at 3 months with epidural injection of PRP compared to steroids.*



Study or Subgroup	therapy Mean	therapy SD	therapy Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, Random, 95% CI
Becker at al	11.7	9.2	32	11.1	7.1	27	35.3%	0.07 [-0.44 , 0.58]
Godek et al	9.65	6.65	40	9.91	10.09	46	39.5%	-0.03 [-0.45 , 0.39]
Wongjarupong et al	15.07	7.79	15	21.3	5.21	15	25.2%	-0.91 [-1.67 , -0.16]
Total (Wald[a])			**87**			**88**	**100.0%**	**-0.22 [-0.74 , 0.31]**

Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable
Heterogeneity: Tau² (REML[b]) = 0.13; Chi² = 4.93, df = 2 (P = 0.09); I² = 63%

Footnotes
[a]CI calculated by Wald-type method.
[b]Tau² calculated by Restricted Maximum-Likelihood method.

Fig. 18B. *Change in function at 6 months with epidural injection of PRP compared to steroids.*

Fig. 18. *Analysis of change of function with epidural injection of PRP compared to steroids.*

more effective than corticosteroids and comparable to radiofrequency neurotomy at six-month follow-up.

Manchikanti et al (19) conducted a systematic review of regenerative medicine therapies for axial spinal pain of facet joint origin with meta-analysis following PRISMA guidelines (421). Qualitative analysis included 4 RCTs (473,475-477) and 6 observational studies (7,432,435,478-481).

Among the RCTs, all evaluated PRP; one cervical facet joint injection trial (476) was negative, while all lumbar facet joint single-injection studies were positive (473,475,477). In the observational studies, one involved adipose tissue (481), 4 used PRP (432,435,478-480), and 2 used MSCs (7,481). One cervical facet PRP study was included (478,479). Many studies utilized a functional spine unit approach, complicating isolated evaluation of facet joint injections. For example, Kirchner and Anitua (432) combined intradiscal, facet, and transforaminal epidural injections; Machado et al (435) injected facet joints, discs, epidural space, and paravertebral muscles; Barbieri et al (480) injected discs, epidural space, facet joints, and sacroiliac joints. Among MSC studies, Rothoerl et al (481) injected only facet joints, whereas Atluri et al (7) used bone marrow concentrate in discs, facets, spinal nerves, and sacroiliac joints. Three PRP studies were positive (432,435,478,479) and one was negative (480). Study characteristics are shown in Tables 14 and 15, with methodologic quality and risk of bias assessed using standardized metrics (Appendix Tables 1-4). All RCTs were included in GRADE certainty assessment (Table 16).

A search for facet joint interventions with regenerative therapies identified a single prospective study by Baltzer et al (482), including 78 patients with chronic facet joint syndrome treated with either PRP or bupivacaine. Multiple weekly injections were administered.

Table 13. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence assessing epidural injections of PRP and derivatives.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
Gupta et al, 2024 (456)	RCT, AC	Low	NS	NS	NS	Low	46 patients Epidural injection of PRP n = 23 Epidural injection utilizing Corticosteroids n = 23	Moderate Moderate impact showing pain relief of 75% or higher at 6-month follow-up, along with improvement in other parameters or function. Suboptimal PRP Positive PRP trial	Moderate
Jayasoorya et al, 2024 (462)	RCT, AC	Low	NS	NS	NS	Low	64 patients Epidural injection of PRP n = 32 Epidural injection utilizing Corticosteroids n = 32	Low • Significant improvement in pain relief at 3 months in PRP group compared to corticosteroid group • There were also clinically significant differences with ODI questionnaire and SLRT scores Suboptimal PRP Positive PRP trial	Moderate
Wongjarupong et al, 2023 (464)	RCT, AC	Low	NS	NS	NS	Low	30 patients PRP Group n = 15 Triamcinolone Group n = 15	Low • The results showed significant improvement with leg VAS. • Results also showed clinically relevant reductions in Back VAS and ODI, even though it did not reach statistically significant difference Suboptimal PRP Positive trial of PRP	Moderate
Godek et al, 2023 (465)	RCT, AC	Low	NS	NS	NS	Low	100 patients Group A: Epidural interlaminar approach with ultrasound-guided injections utilizing ACS (Orthokine) n = 50 Group B: Perineural injection with ultrasound guided injections utilizing ACS (Orthokine) n = 50	Low • There was no significant difference with either approach. This was a technical comparison. There were 2 injections 7 days apart • The volumes of injections were similar for interlaminar and transforaminal group which is considered as very high Orthokine not available in U.S. Positive trial of ACS (Orthokine) in lumbar degenerative disc disease	Moderate

Table 13 cont. *Evidence profile using randomized controlled trials of interventions for the same outcome and similar certainty of evidence assessing epidural injections of PRP and derivatives.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
Singh et al, 2023 (463)	RCT, AC	Low	NS	NS	NS	Low	45 patients Group 1: PRP n = 23 Group 2: Steroid with local anesthetic n = 22	Moderate • At 6-month follow-up superior results were demonstrated with PRP with pain rating, as well as GPE scores. Suboptimal PRP Positive trial of PRP	Moderate
Saraf et al, 2023 (457)	P, RCT, DB	Low	NS	NS	NS	Low	60 patients Single transforaminal injection of PRP n = 29 Single transforaminal injection of steroid n = 31	Moderate • PRP showed significantly better outcomes at 3 and 6 months in reference to pain, function, and SLRT Positive PRP trial	Moderate
Xu et al, 2021 (461)	RCT, AC	Low	NS	NS	NS	Low	124 patients Ultrasound guided transforaminal injection n = 61 Ultrasound guided epidural steroid injection n = 63	Moderate • Both groups showed significant improvements in VAS and ODI, as well as other parameters compared to baseline; however, there was no difference between the groups Imaging with ultrasound Neutral trial of PRP	Low
Ruiz-Lopez & Tsai, 2020 (460)	RCT, AC	Low	NS	NS	NS	Low	50 patients Caudal epidural injections of LR-PRP or corticosteroid administered under fluoroscopic guidance	Low • Positive trial of PRP of caudal epidural compared to corticosteroids Suboptimal PRP Positive	Moderate
Becker et al, 2007 (459)	RCT, AC	Very Low	NS	NS	NS	Low	84 patients Epidural perineural injection with ACS (Orthokine) n = 32 Epidural perineural triamcinolone 10 mg n = 25 Epidural perineural triamcinolone 5 mg n = 27	Low • ACS (Orthokine) was superior to triamcinolone at 26 weeks • The results of epidurals are as expected to deteriorate after several weeks after 22 weeks. Orthokine not available in U.S. Positive trial of ACS (Orthokine)	Moderate

AC = active controlled; ACS = autologous conditioned serum; DB = double-blind; GPE = Global Perceived Effect; NS = Not serious; ODI = Oswestry Disability Index; PRP = platelet-rich plasma; P = prospective; RA = randomized; SLRT = straight leg raising test; VAS = Visual Analog Scale

Table 14. *Study characteristics of randomized controlled trials assessing intraarticular facet joint injections of PRP.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients and Interventions**	**Intervention Group**	**Comparator**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
PLATELET-RICH PLASMA								
Wu et al, 2017 (473) RA, AC Quality Scores: Cochrane = 13/13 IPM-QRB = 37/48	n = 46 Lumbar facet joint syndrome Biologic Used: PRP Group A = PRP Group B = LA with steroids Selection Criteria: Clinical assessment Single intraarticular injections Radiographic evidence	Group A: Intraarticular injection with PRP	Group B: Intraarticular injection with local anesthetic/ corticosteroid	VAS at rest and during flexion RMDQ ODI Modified MacNab criteria for pain relief and applications of post-treatment drugs All outcome assessments were performed immediately after and at 1 week, 1-, 2-, 3-, & 6-months after treatment	There were significant differences between the 2 groups in VAS, ODI ($P < 0.05$) For group A, subjective satisfaction was progressive over time with significant long-term improvement There were no treatment-related complications in either group during follow-up	This is the first randomized control, blinded, trial with diagnosis confirmed by the single intraarticular diagnostic block Outcomes with PRP are superior to corticosteroid injections Patient satisfaction also increased gradually for PRP group, whereas it decreased for steroid group	This is an active control trial with no placebo group A single diagnostic block was performed with intraarticular local anesthetic injection, which is not ideal to achieve appropriate diagnosis	Positive for PRP Autologous PRP is a superior treatment option with longer duration efficacy compared to intraarticular steroid injections Both autologous PRP and local anesthetic/ corticosteroid for intra-articular injection are effective
Kotb et al, 2022 (475) P, RA, comparative, single blinded study, AC Quality Scores: Cochrane = 11/13 IPM-QRB = 32/48	n = 30 Lumbar facet joint disease Biologic Used: PRP Group I – PRP injection Group II – Intraarticular injection with steroid Selection Criteria: Clinical evaluation MRI findings of lumbar facet joint synovitis No diagnostic blocks	Intraarticular injection of autologous PRP	Intraarticular injection of corticosteroids	Low back pain VAS RMDQ ODI 3 months	Both groups showed a significant improvement in all parameters at follow-up after 3 months PRP injections promoted better performance in terms of MRI synovitis grade in all lumbar facet joint levels compared to corticosteroid injections	Randomized controlled trial, first of its nature to study the role of PRP versus corticosteroids in the treatment of synovitis Multiple outcome parameters were utilized	A single blind study, with no placebo group There were no diagnostic blocks performed to accurately predict the diagnosis of facet joint pain Short-term follow-up	Positive for PRP The results show significant improvement compared to corticosteroids with PRP intraarticular injections The study results provide hypothetical improvement requiring additional studies to confirm the results

Table 14 cont. *Study characteristics of randomized controlled trials assessing intraarticular facet joint injections of PRP.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients and Interventions**	**Intervention Group**	**Comparator**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Allison et al, 2024 (476) RA, DB, C, AC Quality Scores: Cochrane = 13/13 IPM-QRB = 40/48	n = 40 Cervical facetogenic pain Biologic Used: PRP Selection criteria: Clinical criteria Positive response to dual cervical medial branch blocks	Intraarticular injection of PRP	Intraarticular corticosteroid injections	NRS PSEQ NDI 1-, 3-, & 6 months post intervention	Low-concentrate PRP and corticosteroid injections had similar effects on cervical facetogenic pain intensity over a 6-month period post injection as demonstrated by a non-significant group-by-time interaction for NRS scores ($P > 0.05$) Both groups showed a statistically significant decrease in cervical facetogenic pain intensity 1 month post treatment compared with baseline ($P = 0.02$), while the PRP group also demonstrated a clinically significant decrease in pain intensity at the same time point There was no significant difference in mean 2-point reduction in PRP and corticosteroid groups at any time	The first randomized controlled trial evaluating intraarticular PRP in the cervical spine. Further, selection criteria was rigorous with dual medial branch blocks Rigorously conducted study	There was no placebo group Low objectives for improvement with less than 40% of the patients achieving a 2-point reduction in their pain at one-month follow-up in the steroid group	Negative for PRP Despite excellent design and rigorous methodology, the study does not show significant difference between corticosteroids and PRP Further, only 63% of patients achieved a 2-point reduction at one-month follow-up with no significant improvement at 3-month follow-up This is an excellent study for future evaluations

Table 14 cont. *Study characteristics of randomized controlled trials assessing intraarticular facet joint injections of PRP.*

Study **Study Characteristic** **Methodological Quality Scoring**	**Number of Patients and Interventions**	**Intervention Group**	**Comparator**	**Outcome Measures and Time of Measurement**	**Results**	**Strengths**	**Weaknesses**	**Conclusions**
Cauchon et al, 2024 (477) RA, triple blind, C, AC Quality Scores: Cochrane = 13/13 IPM-QRB = 42/48	n = 50 Lumbar facet joint pain Biologic Use: PRP Selection criteria: Clinical criteria Positive response to dual lumbar intraarticular injections with 80% pain relief	n = 25 In each joint, 1 mL of non-activated PRP was injected	n = 25 0.5 mL of triamcinolone acetonide 40 mg/mL mixed with 0.5 mL of sodium chloride solution or normal saline into each joint	NRS ODI Treatment satisfaction (with modified MacNab criteria) Quality of life (SF-36) Primary outcome was the percentage of patients improving function above MCID Secondary outcome was the percentage of participants with > 50% NRS improvement, satisfaction to treatment and mean score improvement 1-, 3-, and 6-months	The proportion of participants improving their ODI scores above the MCID. The proportion of participants with > 50% NRS improvement, and mean ODI scores were significantly different between groups in favor of PRP at 6 months. Modified MacNab satisfaction scale, NRS and SF36 mean scores were not statistically different between the groups, but all followed the same patterns: the corticosteroid group had a greater improvement at one-month, but both groups were equivalent at 3 months, and the PRP group had a greater improvement at 6 months.	The first randomized, controlled, triple blinded study with strict parameters and diagnosis following established criteria in the United States with 80% pain relief and dual controlled diagnostic blocks. Shows definitive results with improvement in lumbar facet joint pain with PRP injections.	Not a placebo controlled study.	Positive for PRP Patients receiving PRP showed definitive improvement significantly better than corticosteroids at 6-month follow-up.

AC = active controlled; DB = double blind; C = controlled; IPM-QRB = Interventional Pain Management techniques – Quality Appraisal of reliability and Risk of Bias Assessment; LA = local anesthetic; MCID = minimal clinically important difference; MRI = magnetic resonance imaging; NDI = Neck Disability Index; NRS = Numeric Rating Scale; ODI = Oswestry Disability Index; P = prospective; PRP = platelet-rich plasma; PSEQ = Pain Self-Efficacy Questionnaire; RA = randomized; RMDQ = Roland Morris Disability Questionnaire; SF-36 = Short Form survey 36; VAS = Visual Analog Scale

Table 15. *Study characteristics of non-randomized and observational studies assessing intraarticular facet joint injections of MSCs and PRP.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
PLATELET-RICH PLASMA								
Kirchner & Anitua, 2016 (432) O, R, pilot study Quality Scores: ROBINS-E = 4/7 IPM-QRBNR = 27/48	n = 86 Lumbar disc degeneration Biologic Used: PRGF-Endoret Selection Criteria: Clinical assessment Imaging No diagnostic blocks	One intradiscal, one intraarticular facet, and one transforaminal epidural injection	None	VAS over time 1-, 3-, & 6-months	Pain reduction after PRGF- Endoret injections showed statistically significant drop from 8.4 ± 1.1 before the treatment to 0.8 ± 1.7 at 6-month follow-up At the end of 6 months, 91% of patients showed an excellent score, with 8.1% showing moderate improvement, and 1.2% were inefficient score group	Reasonably large sample of 86 patients	Only a 6 month follow up The injection was into the disc plus intraarticular and transforaminal epidural injections. Consequently, specificity has been lost	Positive PRGF study The results of PRGF injection into discs and facet joints showed reduction of the VAS over time The study ended at 6 months with 91% of the patients showing an excellent score, 8.1% showing moderate improvement, and 1.2% showing lack of response
Smith et al, 2022, 2023 (478,479) P, O Quality Scores: ROBINS-E = 7/7 IPM-QRBNR = 27/48	n = 44 Chronic whiplash-associated disorders and cervical facet joint mediated pain Biologic Used: PRP Forty-four people (82% female, mean age ¼ 45.2 (range: 25–71) years) underwent cervical facet joint PRP. Nine people received repeat PRP interventions. Thirty-five people provided 12-month data. Selection Criteria: Clinical evaluation Imaging Single medial branch blocks with criterion standard of 80% pain relief or greater than 50% relief of pain with significant improvement in activities of daily living in the 6-hour post procedure.	Cervical facet joint PRP injection	None	NPRS NDI 3-, 6- & 12- months	There was a significant improvement in pain and disability following PRP (and possibly adjunct physiotherapy) received during this time period At 12-months, 53% of people exceeded MCID for pain, reporting a mean improvement of 66% (95%CI: 55–77%) on the NPRS For NDI scores, 69% of people exceeded MCID, reporting a mean improvement of 48% (95%CI: 38–58%) 37% of people reported greater than 50% relief of pain 12-months post-cervical facet joint PRP	One of the early studies evaluating cervical facet joint pain A prospective case series Diagnosis was confirmed by a single medial branch block even though not the most optimal, in conjunction with clinical examination and imaging Reasonably long term follow-up. Methodologically excellent study	Not a randomized controlled trial Even though results are positive with MCID for pain and function, when 50% relief of pain was evaluated only 37% of the patients reported 50% pain relief at 12 months post cervical facet joint PRP	Positive PRP study In people with chronic whiplash associated disorders and facet-mediated pain, our long-term data suggests that PRP (and possibly adjunct physiotherapy) is effective A controlled study is warranted to evaluate the efficacy of PRP

Table 15 cont. *Study characteristics of non-randomized and observational studies assessing intraarticular facet joint injections of MSCs and PRP.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Machado et al, 2022 (435) P, case series Quality Scores: ROBINS-E = 4/7 IPM-QRBNR = 24/48	n = 46 Chronic low back pain Biologic Used: PRP Selection Criteria: Clinical findings Imaging No diagnostic blocks	PRP into the facet joints, intervertebral discs, epidural space and/or paravertebral muscles	None	VAS RMDQ 52 weeks	Mean VAS was reduced from 8.48 to 5.17 and mean RMDQ from 18.0 to 10.98 at 12 weeks ($p < 0.001$) These statistically significant improvements were sustained over 52 weeks No adverse effects were observed	Prospective case series with relatively long-term follow of one-year Well-designed following the standard protocol items, recommendations for interventional trials SPIRIT checklist. The study also shows that patients who received injections of 3 structures have shown better improvement.	Non-randomized design Multiple structures injected at the same time confounding the diagnosis and treatment	Positive PRP study PRP approach demonstrated clinically favorable results and may be a promising treatment for chronic low back pain
Barbieri et al, 2022 (480) P, case series Quality Scores: ROBINS-E = 4/7 IPM-QRBNR = 23/48	n = 32 Chronic low back pain Biologic Used: PRGF Selection Criteria: Clinical assessment Imaging No diagnostic blocks	PRGF was injected into the intervertebral disc, epidural space and/or facet and sacroiliac joints	None	VAS ODI PGIC 3 and 6 months	Overall, the patients did not ameliorate after PRGF treatment, although 8 patients showed an algo-functional improvement They were mainly males treated at 2 sites who were younger, less sedentary and with fewer musculoskeletal co-morbidities than the nonresponders	This study does not possess any strengths other than being another publication with a prospective case series	Prospective case series without a comparator	Negative PRGF study Overall, the patients did not ameliorate after PRGF treatment, even though 8 of 32 patients showed an algo-functional improvement
MESENCHYMAL STEM CELLS								
Rothoerl et al, 2023 (481) O Quality Scores: ROBINS-E = 7/7 IPM-QRBNR = 27/48	n = 37 Facet joint syndrome Biologic Used: Autologous stem cells Selection Criteria: Clinical assessment Imaging Single diagnostic medial branch block with ropivacaine	Adipose derived autologous stem cells were injected into facet joints	None	VAS ODI 1 week, 1 year, & 5 years	Every patient reported improved VAS pain at any follow-up (1 week, 1 year, & 5 years) with ADRC compared to the baseline	Stem cell usage from adipose has not been described in facet joint pain in the past This is the first publication with a long-term follow-up	Non-randomized design	Positive study of stem cells Data indicates that facet joint syndrome patients treated with unmodified adipose tissue-derived regenerative cells experienced improved quality of life in the long term

Table 15 cont. *Study characteristics of non-randomized and observational studies assessing intraarticular facet joint injections of MSCs and PRP.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients and Interventions	Intervention Group	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Atluri et al, 2022 (7) P, open-label, NR, parallel-controlled, 2-arm exploratory study Quality Scores: ROBINS-E = 4/7 IPM-QRBNR = 27/48	n = 80 Low back pain Biologic Used: Autologous bone marrow mesenchymal stem cells Selection Criteria: Severe degenerative disc disease Severe pain with disability not amenable to conservative management	One-time bone marrow concentrate injection into spinal structures (i.e., discs, facets, spinal nerves, and sacroiliac joints), along with conventional treatment	Conventional treatment with nonsteroid anti-inflammatory drugs, over-the-counter drugs, structured exercise programs, physical therapy, spinal injections and opioids, etc., as indicated	ODI NRS EQ-5D-3L GMH GPH Multiple outcomes were assessed with primary outcomes being MCID in ODI scores between the groups and/or a 2-point reduction in pain scores 1-, 3-, 6-, & 12-months	Significant improvement was achieved in functional status measured by ODI, pain relief measured by NRS-11, and other parameters The results showed significant improvements at 12-month follow-up with 67% of the patients in the study group achieving MCID utilizing ODI when compared to 8% in the control group MCID and pain relief of 2 points were significantly different compared to the control group	This is a large prospective, open-label, non-randomized, parallel-controlled, 2-arm comparative study This is the first study evaluating bone marrow concentrate	Non-randomized design Multiple structures were injected at the same time	Positive study of bone marrow concentrate The results of this study showed significant improvement in function and pain relief in 67% of the study group, and achieved MCID for ODI at 12 months, when compared to only 8% in the control group

ADRC = adipose tissue-derived regenerative cells; EQ-5D-5L = EuroQol 5 Dimension; GMH = Global Mental Health; GPH = Global Physical Health; IPM-QRBNR = Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies; MCID = Minimal Clinically Important Difference; NDI = Neck Disability Index; NPRS = Numerical pain rating scale; NR = nonrandomized; NRS = Numeric Rating Scale; O = observational; ODI = Oswestry Disability Index; P = prospective; PGIC = Patient Global Impression of Change; PRGF = plasma rich in growth factor; PRP = platelet-rich plasma; R = retrospective; RMDQ = Roland-Morris Disability Questionnaire; ROBINS-E = Risk of Bias in Non-Randomized Studies of Exposure; SPIRIT = Standard Protocol Items: Recommendations for Interventional Trials; VAS = Visual Analog Scale

PRP infiltrations significantly reduced pain scores compared to baseline up to one year ($P = 0.001$). Oswestry Disability Index scores improved by approximately 50% at 6 months ($P = 0.001$) and were significantly better at one year ($P < 0.01$). The authors concluded that CT-guided leukocyte-poor PRP injections provided substantially better outcomes than intra-articular bupivacaine.

Meta-analysis was not available. Based on qualitative and quantitative evidence, including GRADE certainty assessment, the evidence was deemed Level III, or fair, with a clinical recommendation of moderate certainty.

7.4 Sacroiliac Joint Injections

Key Question 7. The evidence of effectiveness for the use of PRP in sacroiliac joint injections and consensus-based clinical recommendations.

The sacroiliac joint is the largest axial joint in the human body, playing a critical role in stability and in transmitting forces from the upper trunk to the lower extremities (483). Degenerative changes such as osteoarthritis represent progressive disorders of synovial joints caused by an imbalance between joint damage and repair, resulting in pain (484). Inflam-

Table 16. *Evidence profile utilizing GRADE criteria with inclusion of randomized controlled trials for facet joint injections of PRP for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT							Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**			
Wu et al, 2017 (473)	RA, AC	Low	NS	NS	NS	Low	Total = 46 Group A (randomized) intraarticular injection with PRP = 23 Group B (randomized) intraarticular injection with local anesthetic and corticosteroid = 23	Randomized controlled trial with active control design, compared injection of PRP with injection of local anesthetic and corticosteroid. Reasonably well designed. Applicable to clinical practice. Single diagnostic block Positive for PRP	Moderate
Kotb et al, 2022 (475)	RA, SB, AC	Low	NS	NS	NS	Low	Total = 30 Group I PRP injection = 15 Group II Intraarticular injection with steroid = 15	This is a small randomized, single-blinded study with active control design with patients receiving either intraarticular injection of PRP or injection of local anesthetics with corticosteroids providing positive results applicable to clinical practice. No diagnostic block Positive for PRP	Low
Allison et al, 2024 (476)	RA, PC DB	Low	NS	NS	NS	Low	Total = 40 Group I cervical intraarticular injection of PRP = 21 Group II cervical intraarticular injection with corticosteroid = 19	This is a randomized, double blind controlled trial. Very well designed comparing cervical intraarticular facet joint injection of PRP with intraarticular corticosteroid injections showing negative results. Negative for PRP	Very low
Cauchon et al, 2024 (477)	RA, AC, TB	Low	NS	NS	NS	Low	Total = 50 Group I lumbar intraarticular injection of PRP = 25 Group II lumbar intraarticular injection with corticosteroid = 25	This is a randomized, triple blind, active control trial, extremely well designed comparing lumbar intraarticular facet joint injection of PRP with intraarticular corticosteroid injection showing positive results with very well performed study with significantly superior results. Positive for PRP	Moderate

AC = active controlled; DB = double-blind; NS = Not serious; PC = placebo controlled; PRP = platelet-rich plasma; RA = randomized; SB = single-blind; TB = triple blind

matory sacroiliac joint pain arises from dysregulated inflammatory responses, involving complex cellular and chemotactic profiles with both inflammatory and catabolic mediators contributing to joint degeneration (483). Additionally, joint hypermobility, a biomechanical dysfunction caused by pelvic ligament laxity or mechanical stress, compromises the sacroiliac joint's capacity to bear axial loads, placing strain on adjacent tissues (485).

The sacroiliac joint is a recognized source of low back and lower extremity pain, alongside the intervertebral discs, nerve roots, and facet joints (38,52,54,62,102,486). However, diagnostic accuracy remains controversial, particularly regarding the utility of intra-articular injections (38,102). Controlled diagnostic block studies implicate the sacroiliac joints in 10% to 25% of low back pain cases unrelated to disc herniation, discogenic pain, or radiculitis (38,41,57,62,102,486).

Management of chronic lumbosacral pain includes conservative approaches such as physical therapy and pharmacological treatments, as well as interventional procedures (2,38-42,44,48-54,85,99-102,219,450,451,469,487-499). Regenerative medicine therapies, including PRP and MSCs, have gained interest for treating spinal disorders, including sacroiliac joint pain, intervertebral disc degeneration, and facet joint dysfunction (10,17,18,95,283,410,413,415-419,439,472,483-485,500-512).

Sanapati et al (17) conducted a systematic review and meta-analysis of regenerative medicine injections for low back pain, including sacroiliac joint injections. They identified one high-quality RCT (510), one moderate-quality observational study (511), and one low-quality case report (512), concluding that the qualitative evidence was Level IV (on a scale of I to V based on a modified evidence grading system). Meta-analysis was not feasible.

Goodwin et al (503), in a qualitative systematic review with pooled analysis, examined 4 clinical trials and 2 case studies. They concluded that although PRP injections appeared beneficial, the evidence did not support their use over the current steroid standard of care.

Burnham et al (504) reviewed PRP for sacroiliac joint pain and identified 3 eligible studies, including one randomized comparative trial and 2 case series. Using the GRADE system, they rated the quality of evidence supporting PRP effectiveness as very low.

Ruffilli et al (506), in a systematic review and meta-analysis of injectable treatments for sacroiliac joint pain, analyzed 43 studies, with 16% involving PRP injections. They reported a failure rate of 26% for steroid injections versus 14% for PRP injections. While early data on PRP appeared promising, the authors concluded that current literature limitations prevent determination of the optimal injectable approach.

Rothenberg et al (483), in a descriptive review, found the evidence for sacroiliac joint PRP to be inconsistent and insufficient to make definitive recommendations.

Although PRP and MSC therapies have a long history in orthopedic injuries, few studies specifically address sacroiliac joint dysfunction. Most research focuses on degenerative intervertebral discs. PRP, first described in the early 1990s as a biological glue, is defined as a platelet concentration above baseline. Platelets deliver growth factors and bioactive molecules essential for proliferation, vessel remodeling, angiogenesis, inflammation modulation, coagulation, and cell differentiation, all contributing to tissue repair and healing (512).

Despite growing evidence supporting PRP and BMC therapies for other axial skeleton applications, including intradiscal and intra-articular injections, significant gaps remain regarding their therapeutic value for sacroiliac joint dysfunction.

Manchikanti et al (21) conducted a systematic review of sacroiliac joint PRP and stem cell injections with meta-analysis following PRISMA guidelines (421). This review included 2 RCTs (291,510) and 3 observational studies (513-515). Using the GRADE framework and qualitative synthesis, the evidence was determined to be Level IV (limited) with a weak recommendation. Study characteristics are shown in Tables 17 and 18, with methodologic quality and risk of bias assessed using standardized metrics (Appendix Tables 1-4). All RCTs were included in GRADE certainty assessment (Table 19).

PRISMA-guided search criteria for sacroiliac joint regenerative injections identified no additional studies beyond those included in the 2025 systematic review by Manchikanti et al (21). Qualitative and quantitative analysis included the 2 RCTs (291,510), with one active-control trial positive and the other negative. Among the observational studies, 2 PRP injection studies were positive (514,515) and one was negative (513). GRADE assessment indicated one study with moderate positive impact and 2 with low positive impact. Consequently, the evidence level was IV (limited), with a clinical recommendation of low.

Burnham et al (504) is particularly notable among previously published systematic reviews. They defined the primary outcome as >50% pain improvement and

Table 17. *Study characteristics of randomized controlled trials assessing the role of PRP injections of sacroiliac joints.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients & Selection Criteria	Sacroiliac Joint PRP Injection	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Singla et al, 2017 (510) RA, Single-blinded, C Quality Scores: Cochrane = 11/13 IPM-QRB = 32/48	40 patients allocated into 2 groups Group P = PRP group (n = 20) Group S = Steroid group (n = 20) Selection Criteria: Clinical examination • Positive provocative test • Imaging	20 patients received 3 mL of leukocyte-free PRP with 0.5 mL of calcium chloride, with a total volume of 3.5 mL, with ultrasound-guided intraarticular sacroiliac joint injection	20 patients received 1.5 mL of methylprednisolone, 40 mg per mL, and 1.5 mL of 2% lidocaine with 0.5 mL of saline, with a total volume of 3.5 mL, with ultrasound-guided intraarticular sacroiliac joint injection	• VAS scores • MODQ scores • SF-12 health survey scores • Complications assessment at 2, 4, & 6 weeks & 3 months • Proportion of pain relief > 50%	PRP injections provided significantly lower VAS with better pain relief at 3 months as compared to steroid injections Effectiveness 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 No adverse events noted	Randomized controlled trial	Active controlled trial with no placebo group Small sample size Short-term follow-up	Positive trial for PRP Results show significantly better improvement with PRP injection compared to steroid injection
Chen et al, 2022 (291) RA, DB, C Quality Scores: Cochrane = 11/13 IPM-QRB = 35/48	26 patients with a positive response of 80% or greater to a single diagnostic block with a fluoroscopically guided intraarticular injection Randomization into 2 groups, either steroid or PRP	Intraarticular sacroiliac joint injection of 0.5 to 1 mL of contrast medium used to confirm in the placement of the needle Following this, PRP group received a single injection of 2 mL PRP	Intraarticular sacroiliac joint injection of 0.5 to 1 mL of contrast medium used to confirm in the placement of the needle Following this, the steroid group received a single injection consisting of a combination of 1 mL of betamethasone sodium phosphate and acetate suspension, 6 mg, per mL and 1 mL of 2% lidocaine	• Level of pain • ODI • Proportion of pain relief > 50% 1, 3, & 6 months	Both groups improved at all time periods – 1, 3, & 6 months At 3 months, 70% of the steroid group patients and 21.4% of PRP group showed significant improvement At 6 months, neither group showed significant improvement No adverse events noted	• Randomized, double blind, clinical trial available • Well performed study with appropriate outcome parameters	Small sample size Active controlled trial	Negative for PRP Even though PRP patients and steroid patients both showed significant improvement, both showed improvement from baseline At 3 months, a significantly higher proportion of patients in steroid group showed better results

C = controlled; DB = double-blind; IPM-QRB = Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment; MODQ = Modified Oswestry Disability Index; ODI = Oswestry Disability Index; PRP = platelet-rich plasma; RA = randomized; SF-12 = 12-Item Short Form Survey; VAS = Visual Analog Scale

Table 18. *Study characteristics of non-randomized and observational studies assessing the role of PRP injections of sacroiliac joints.*

Study Study Characteristic Methodological Quality Scoring	Number of Patients & Selection Criteria	Sacroiliac Joint PRP Injection	Comparator	Outcome Measures and Time of Measurement	Results	Strengths	Weaknesses	Conclusions
Mohi Eldin et al, 2019 (513) P, NR, C Quality Scores: ROBINS-E = 7/7 IPM-QRBNR = _36/48	Total number of patients = 186 124 patients in PRF group 62 patients in PRP group Selection Criteria: • Clinical evaluation with at least 3 positive provocation tests • Diagnostic nerve blocks	A single injection of PRP under fluoroscopic guidance	A single injection of PRF under fluoroscopic guidance	VAS 6-month follow-up	82 of 124 patients were considered as negative in PRF group, whereas 41 of 62 patients were considered negative in PRP patients Overall result appears to be both PRF & PRP were negative No adverse events noted	Nonrandomized comparative evaluation with a relatively large sample size	Nonrandomized study Outcomes criteria not well described	Negative for PRP Only a small proportion of patients showed improvement in both PRF & PRP groups
Wallace et al, 2020 (514) P, NR Quality Scores: ROBINS-E = 5/7 IPM-QRBNR = _25/48	50 patients Selection Criteria: • Clinical signs • Imaging • Clinical evaluation with 3 positive provocative tests No diagnostic blocks were performed	50 received PRP injection with 3 mL of PRP under ultrasound guidance	None	Pain relief with ODI 2 & 4 weeks, 3 & 6 months	The mean reduction in ODI and pain scales was significant at 6 months after injection compared with baseline values No adverse events noted	Performed in a clinical setting with 6-month follow-up	Prospective study performed in a clinical setting Nonrandomized study with relatively small sample	Positive PRP study
Saunders et al, 2018 (515) NR, O Quality Scores: ROBINS-E = 4/7 IPM-QRBNR = 18/48	45 patients compared to the control group receiving hypertonic glucose injections Selection Criteria: • Clinical examination	PRP injection was performed under ultrasound guidance	Prolotherapy injections performed under ultrasound guidance	• VAS RMDQ • Quebec Back Pain Inventory • Clinical tests of sacroiliac joint incompetence	The outcome measures of change in pain scores, improvement in function between the groups was superior for the PRP group All PRP patients experiencing significant improvement in pain score & function The number of injections required was less for the PRP group with mean of 1.6 than the controls with mean of 3.0 No adverse events noted	Prospective, nonrandomized comparative evaluation	Lack of placebo group in a nonrandomized study which may have induced multiple confounding factors	Positive PRP study PRP was described as a viable alternative to hypertonic dextrose injection with significantly better relief at 12-month follow-up

C = controlled; IPM-QRBNR = Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies; NR = nonrandomized; O = observational; ODI = Oswestry Disability Index; P = prospective; PRF = platelet-rich fibrin; PRP – platelet-rich plasma; RMDQ = Roland-Morris Disability Questionnaire; ROBINS-E = Risk of Bias in Non-Randomized Studies of Exposure; VAS = visual analog scale

the secondary outcome as functional improvement of > 30% at 3 or more months post-intervention, consistent with the criteria used in this assessment and those applied by Sanapati et al (17). Unlike the present review, their selection criteria did not impose a minimum patient number. They initially identified 151 publications, with only 3 meeting inclusion criteria, including one randomized comparative trial in which the PRP group had a significantly higher likelihood of achieving > 50% pain improvement at 3 months (510). Pooled pain outcomes from 2 additional studies indicated that approximately 93% of patients achieved > 50% pain improvement; however, both studies included only 14 patients and lacked a comparative group.

In contrast, the current systematic review incorporated 2 RCTs (291,510) and 3 observational studies (513-515), with only one study overlapping with Burnham et al's review (504). The conclusions of Burnham et al (504) align with our findings, indicating that the evidence supporting PRP for sacroiliac joint pain is of very low quality according to the GRADE system. Similarly, Ruffilli et al (506), in a systematic review and meta-analysis, concluded that while PRP data appear promising, the limitations of the current literature prevent a clear determination of the most appropriate injectable approach.

7.5 Functional Spine Unit Injections

Key Question 8. The evidence of effectiveness for the functional spine unit approach and consensus-based clinical recommendations.

While most studies focused on single-structure injections, several investigated multiple injection targets.

In a retrospective pilot study of 86 patients with low back pain, Kirchner and Anitua (432) administered plasma rich in growth factor (PRGF) into multiple lumbar spine structures. Each patient received intradiscal, intra-articular facet joint, and transforaminal epidural injections under fluoroscopic guidance, resulting in statistically significant pain reduction up to 6 months. Atluri et al (7) conducted a prospective nonrandomized trial assessing autologous bone marrow-MSCs for chronic low back pain associated with lumbar spinal degeneration involving multiple anatomical structures. Forty patients in the treatment group received autologous BMC injections into discs, facet joints, sacroiliac joints, and around spinal nerves, tailored to the primary pain source. At 12 months, 67% of patients demonstrated significant improvements in pain and functional outcomes, along with reduced opioid use. This study was the first to demonstrate the benefits of administering bone marrow-MSC injections across multiple structures in a single session for chronic spinal degeneration.

In another prospective case series, 46 patients with chronic low back pain received PRP injections into facet joints, intervertebral discs, epidural space, and/or paravertebral muscles. Across the cohort, mean VAS scores decreased by approximately 35%, and disability scores improved by about 40% at one-year follow-up. Over 80% of participants had radiographic evidence of more than one abnormality on MRI, including facet joint arthropathy, spinal canal stenosis, intervertebral disc disease, and paravertebral muscle atrophy. This study highlighted the utility of multitarget PRP injections in addressing multiple pain generators (435).

Table 19. *Evidence profile using randomized controlled trials and nonrandomized or observational studies for sacroiliac injections of PRP for the same outcome and similar certainty of evidence.*

CERTAINTY ASSESSMENT								Number of Patients	Impact	Certainty
Study	**Study Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**				
Singla et al, 2017 (510)	RA, single blinded, C	Moderate	NS	NS	NS	Low		40	Positive	Moderately positive
Chen et al, 2022 (291)	RA, DB, C	Moderate	NS	NS	NS	Low		26	Negative	Moderately negative
Mohi Eldin et al, 2019 (513)	P, NR, C	High	NS	S	S	Very low		186	Negative	Moderately negative
Wallace et al, 2020 (514)	P, NR	Very high	S	S	S	Very low		50	Positive	Low positive impact
Saunders et al, 2018 (515)	NR, O	Very high	S	S	S	Very low		45	Positive	Low positive impact

C = controlled; DB = double-blind; MSC = mesenchymal stem cells; NR = nonrandomized; NS = Not serious; O = observational; P = prospective; RA = randomized; S = serious

Most published studies on spinal orthobiologics primarily focus on degenerative disc disease. Understanding the spine's biomechanical dynamics and the distribution of load across various structures clarifies that most patients with chronic low back pain have multiple pain generators rather than a single source. Consequently, a comprehensive treatment strategy that simultaneously targets these pain generators and addresses the functional spine unit (FSU) is essential for optimizing patient outcomes.

Williams et al (516) reported a case series demonstrating the safety and efficacy of autologous concentrated platelet product injections and prolotherapy in 14 patients with neck pain using an FSU-based treatment protocol. Patients with axial neck pain, with or without radiculopathy, received multiple injections targeting the cervical facet joint, including the cervical facet capsule, supraspinous and interspinous ligaments, and cervical epidural space. The results showed clinically significant improvements in pain and functional outcomes at 24 months, supporting the FSU treatment paradigm and its potential application in managing spinal pain by addressing ligamentous laxity, intra-articular facet arthritis, and nerve root irritation.

7.6 Summary of Evidence

The evidence for intradiscal injections, epidural injections, facet joint injections, sacroiliac joint injections, and multitarget injections using an FSU approach is summarized here. Evidence is derived from randomized and nonrandomized studies and synthesized based on study quality, risk of bias, qualitative and quantitative analyses when available, and the GRADE framework.

7.6.1 Intradiscal Injections

PRP: **Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate**

BMAC: **Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate**

7.6.2 Epidural Injections (PRP)

Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate

7.6.3 Facet Joint Injections (PRP and MSCs)

Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Moderate

7.6.4 Sacroiliac Joint Injections (PRP)

Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Low

7.6.5 Functional Spine Unit Injections

Evidence Level: Very Low; Consensus-Based Clinical Recommendation: Low

8.0 Current Guidelines for Biologics in Industry and Regulatory Agencies

Key Question 9. What are the current guidelines for biologics?

8.1 FDA/WHO as Regulatory Agency for Biologic Therapies

Biologics are more complex than chemically synthesized drugs due to their structural heterogeneity and interactions with biological systems. Each biologic's development and production processes vary because they are derived from living organisms. As new therapies emerge and evolve, maintaining regulatory oversight is essential to ensure the safety, efficacy, and quality of these biologics. The FDA and World Health Organization (WHO) play critical roles in regulating biologic therapies. Currently, biologics are used in pain management for conditions such as osteoarthritis, neuropathic pain, and chronic pain syndromes.

The FDA provides a Biologics Licensing and Approval Process (BLA), which requires a Biologics License Application to approve biologics. A BLA can be submitted by any legal person or entity involved in the manufacture of the biologic or an applicant who assumes responsibility for ensuring that the product and establishment comply with required standards. The BLA process includes clinical testing and a thorough regulatory review to demonstrate the biologic's safety, efficacy, and quality. Once these criteria are met, the FDA grants approval. After approval, the FDA continues to monitor biologics through post-market surveillance programs to identify any adverse effects or long-term safety concerns related to their use (517).

The FDA regularly publishes guidance documents outlining regulatory expectations for the development and approval of biologics. In 2018, the FDA introduced the Biosimilars Action Plan (BAP) to promote innovation and competition in the biological product market, streamline the development and approval of biologics, and enhance understanding of biologics among patients, clinicians, and payers. The FDA's Patient-Focused Drug Development (PFDD) initiative also encourages incorporating patient perspectives into the drug development process. The FDA provides additional guidance for preclinical testing, clinical trial designs, and long-term patient monitoring for cell and gene therapies that fall under Human Cells, Tissues, & Cellular & Tissue-Based Products (HCT/Ps). The FDA enacted the Regenerative Medicine Advanced Therapy (RMAT) Designation in 2017 to expedite the development of pathways for regenerative therapies that show potential in early trials.

The WHO is responsible for the global regulation of biologic therapies, including those used for pain management, by developing guidelines and standards for its member states. Its key responsibilities include establishing international standards for biologics' production and quality control, assisting countries to strengthen regulatory oversight to ensure that biologics meet safety and efficacy standards, and evaluating and listing biologic products that meet WHO standards to facilitate access. The WHO has developed quality assurance guidelines for producing biologics, ensuring that those used in clinical practice meet quality and safety standards, which are crucial for patient safety. The WHO's Prequalification Program assesses the quality and safety of medicines, including biologics, allowing manufacturers to gain recognition for their products (518,519).

In addition, the FDA and WHO collaborate on various regulatory initiatives concerning standards for biologics. This collaboration includes participation in forums such as the International Conference on Harmonization (ICH), which addresses the regulatory oversight of biologics. Their joint efforts are significant in harmonizing regulatory standards, guideline development, and global health initiatives.

8.2 Human Cells, Tissues, & Cellular & Tissue-Based Products (HCT/Ps)

The FDA regulates HCT/Ps under 21 CFR Part 1271 with a risk-based approach to ensure they are safe for patient use. The guidelines have 2 sections: Section 361 HCT/Ps (minimally regulated) and Section 351 HCT/Ps (subject to more stringent regulation) (362).

Products regulated under Section 361 of the Public Health Service (PHS) Act are subject to less stringent oversight because they are considered minimally manipulated. Examples include skin grafts, bone grafts, and corneal transplants. These products are used in a homologous manner to their natural function. Minimal manipulation means the processing does not alter the original characteristics of the cells or tissues. No premarket approval is needed for these products, but they must meet Good Tissue Practices (GTP), which ensure the safe handling, testing, and storage of HCT/Ps.

Products regulated under Section 351 of the PHS Act require a Biologics License Application (BLA). These include cell therapies where stem cells are expanded or differentiated in culture, gene therapies, and some

tissue-engineered products. These products must undergo pre-market approval and clinical trial phases. cGMP applies, and these products require stringent controls over the manufacturing, packaging, and distribution of HCT/Ps. They are evaluated for safety, efficacy, and quality, and manufacturers must comply with extensive post-market surveillance to monitor long-term outcomes and adverse events.

The FDA mandates that HCT/Ps be used for their homologous function, meaning the product must serve a purpose in the body consistent with its natural role. For example, cartilage tissue should be used to repair cartilage, not for treating other tissues or organs. For cell and gene therapies categorized under HCT/Ps, the FDA provides additional guidance on preclinical testing, clinical trial design, and long-term patient monitoring. In 2017, the FDA introduced the RMAT Designation to expedite development pathways for regenerative therapies that demonstrate potential in early clinical trials.

MSCs are widely used for their regenerative potential in conditions such as osteoarthritis, degenerative disc disease, and tendon injuries. They are considered minimally regulated by the FDA. PRP therapy is used for joint pain, tendon injuries, and discogenic back pain and is considered a Section 361 HCT/P when used homologously. Amniotic tissue-derived products treat chronic wounds, joint injuries, and orthopedic conditions. These are typically considered minimally manipulated under FDA Section 361 as long as they are used homologously. BMAC, which contains a mixture of stem cells, growth factors, and other regenerative cells from bone marrow, has been employed for intradiscal injections to treat low back pain and knee osteoarthritis. Due to its more than minimal manipulation, stringent FDA guidelines under Section 361 apply to BMAC's use in regenerative therapies.

8.3 Minimal Manipulation

Section 1271.10(a)(1) (21 CFR 1271.10(a)(1)) provides that one of the criteria for an HCT/P to be regulated solely under Section 361 of the PHS Act and the regulations in Part 1271 is that the HCT/P is minimally manipulated (13,362). As defined in 21 CFR 1271.3(f), minimal manipulation means:

1. For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement.
2. For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

The FDA noted that if information does not exist to show that the processing meets the definition of "minimal manipulation," the FDA considers the processing of an HCT/P to be "more than minimal manipulation" and therefore ineligible for regulation solely under Section 361 of the PHS Act and 21 CFR Part 1271 (13,362).

Section 1271.3(f) provides 2 definitions of "minimal manipulation," one for structural tissues and one for cells or nonstructural tissues. For structural tissue, minimal manipulation means that the processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to its utility for reconstruction, repair, or replacement (21 CFR 1271.3(f)(1)). For cells or nonstructural tissues, minimal manipulation means that the processing of the HCT/P does not alter the relevant biological characteristics of cells or tissues (21 CFR 1271.3(f)(2)).

Original relevant characteristics of structural tissues generally include properties of that tissue in the donor that contribute to the tissue's function or functions. Similarly, relevant biological characteristics of cells or nonstructural tissues generally include properties of the cells or nonstructural tissues within the donor that contribute to the cells' or tissue's function(s). Processing that alters the original characteristics of the HCT/P raises increased safety and effectiveness concerns because there is less basis to predict the product's function after transplantation (362). Thus, the determination of whether an HCT/P is minimally manipulated is based on the effect manufacturing has on the original relevant characteristics of the HCT/P as it exists within the donor, not on its intended use in the recipient.

Processing is defined as any activity performed on an HCT/P other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage (21 CFR 1271.3(ff)). Processing also includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization (362).

Tissues that physically support or serve as a barrier or conduit, connect, cover, or cushion in the donor are generally considered structural tissues for determining the applicable regulatory definition (e.g., bone, skin).

Adipose tissue is a structural tissue that can be applied to the HCT/P regulatory framework. Adipose tissue is typically defined as a connective tissue composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed with small blood ves-

sels, divided into lobes and lobules by connective tissue septa (362). Additionally, adipose tissue contains other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and macrophages (362). Adipose tissue provides cushioning and support for different tissues, including the skin and internal organs, stores energy in the form of lipids, and insulates the body, among other functions. While adipose tissue has multiple functions, because it predominantly comprises adipocytes and surrounding connective tissues that provide cushioning and support to the body, the FDA considers adipose tissue a structural tissue for applying the HCT/P regulatory framework.

To evaluate whether the processing of adipose tissue meets the regulatory definition of minimal manipulation, one should consider whether the processing alters the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support (Fig. 19). An opposing view may consider the presence of stem cells within adipose tissue as an indication that this tissue also functions as a repository for regenerative factors.

8.4 Homologous Use

Section 1271.10(a)(2) (21 CFR 1271.10(a)(2)) provides that one of the criteria for an HCT/P to be regulated solely under Section 361 of the PHS Act and the regulations in Part 1271 is that the "HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."

As defined in 21 CFR 1271.3(c), homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic functions in the recipient as in the donor. This criterion reflects the FDA's conclusion that there would be increased safety and effectiveness concerns for HCT/Ps intended for a non-homologous use, because there is less basis for predicting the product's behavior. In contrast, HCT/Ps for homologous use can reasonably be expected to function appropriately (assuming all other criteria are also met) (13,362).

In applying the homologous use criterion, the FDA determines the intended use of the HCT/P as reflected by the labeling, advertising, and other indications of a manufacturer's objective intent, and then applies the homologous use definition.

Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor (21 CFR 1271.3(c)), including when such cells or tissues are for autologous use. Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues perform one or more of the same basic functions in the recipient as they did in the donor. Recipient cells or tissues that may not be identical to the donor's cells or tissues can also meet the homologous use criterion if they perform one or more of the same basic functions in the recipient as in the donor (13,362).

For the purpose of applying the HCT/P regulatory framework, the same basic function or functions of HCT/Ps are considered those basic functions that the HCT/P performs in the donor's body, which, when transplanted, implanted, infused, or transferred, the HCT/P would be expected to perform in the recipient. The HCT/P in the recipient does not need to perform all of the basic functions it performed in the donor to meet the definition of homologous use. However, to meet the definition, any of the basic tasks that the HCT/P is expected to perform in the recipient must be a basic function that the HCT/P performed in the donor.

Using an HCT/P from adipose tissue for the repair, reconstruction, replacement, or supplementation of adipose tissue would be considered a homologous use. In such situations, the FDA considers the HCT/P from adipose tissue to be performing the same basic function in the recipient as in the donor. In contrast, using an HCT/P from adipose tissue to treat a degenerative, inflammatory, or demyelinating disorder would generally be considered a non-homologous use. Figure 19 illustrates how manufacturers and healthcare providers should apply the criteria outlined in 21 CFR 1271.15(b) and 1271.10(a) for HCT/Ps (362).

8.5 Regulatory Scope and Compliance Policy

This guidance applies only to products and establishments subject to the FDA's regulations in 21 CFR Part 1271. Establishments that meet the same surgical procedure exception in 21 CFR 1271.15(b) are not subject to the FDA's regulations in 21 CFR Part 1271.

This guidance also does not apply to products that fall outside the definition of HCT/P in 21 CFR 1271.3(d). For example, PRP (blood taken from an individual and given back to the same individual as PRP) is not an HCT/P under Part 1271 because it is a blood product. Accordingly, the FDA does not apply the criteria in 21 CFR 1271.10(a) to PRP, and PRP is outside the scope of this guidance.

8.6 FDA's Comprehensive Framework for Regenerative Medicine

As described by Marks and Gottlieb (13), the FDA recognizes the time and effort required to create regulatory submissions and the impact that working through the regulatory process can have on the timelines for developing innovative products. Consequently, in November 2017, building on existing policy and emerging scientific opportunities, the FDA released a comprehensive framework for the oversight of regenerative medicine to help the field advance. This regulatory framework is articulated in 2 final and 2 draft guidance documents, as shown in Table 20 (13).

The FDA's new policy framework more clearly describes the distinctions for regenerative medicine developers between therapies that require premarket authorization and those that do not. It provides clear criteria for minimal manipulation and homologous use, as well as a risk-based compliance and enforcement policy as part of the overall regulatory framework.

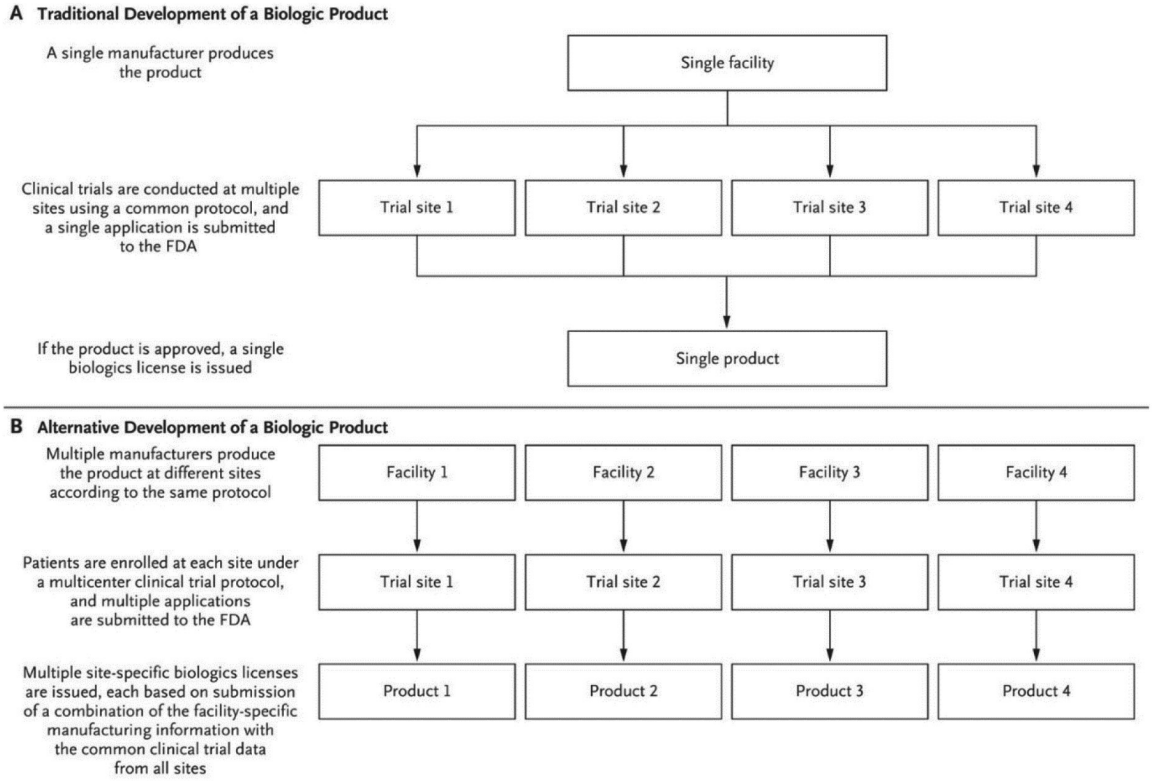


Fig. 19. *Traditional versus alternative development of a biologic product.*
In the traditional development pipeline (Panel A), a single manufacturer produces the product at a single manufacturing facility and sponsors the clinical trials, which are conducted at multiple clinical sites. The manufacturer ensures that the product is manufactured consistently with appropriate quality control for use at each site and that it is administered pursuant to the protocol. The manufacturer then collects and analyzes the data from the clinical trials and submits a biologics licensing application to the Food and Drug Administration (FDA). If the product is approved, the manufacturer then receives a biologics license to produce and distribute the product. As an alternative to this process (Panel B), multiple manufacturers, which may be individual physicians or groups of physicians, enter into a cooperative development agreement. These manufacturers then produce the product at different sites according the same protocol, which includes appropriate quality-control procedures to help ensure consistency between different lots produced at different sites. Patients are enrolled at each of the sites that are manufacturing the product in a multicenter clinical trial protocol. Once the data from the multicenter trial are analyzed to evaluate the safety and efficacy of the product, the individual physicians or groups of physicians submit a biologics licensing application that includes the manufacturing protocol used, the clinical data obtained at the individual site, and the results of the multicenter clinical trial showing safety and efficacy. This ultimately results in the issuance of a site-specific biologics license for the product made by each physician or group of physicians.
Source: Marks P, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. *N Engl J Med* 2018 378:954-959 (13).

Table 20. *Four guidance documents describing the regenerative medicine framework.**

Document	Summary	Example
Same Surgical Procedure Exception under 21 CFR 12.71.15(b): Questions and Answers Regarding the Scope of the Exception -- Final	Addresses the criteria required for the exception, the types of procedures generally considered to be the same surgical procedure, and what processing steps can be undertaken to still meet the exception. In essence, this guidance clarifies how the regulations apply in order to facilitate the optimal care of patients undergoing surgical procedures.	A situation in which this guidance would apply is when a piece of the skull is removed for decompression after traumatic head injury. The bone may be minimally processed, stored, and then returned to the patient a few weeks later when the acute event is over, without the need for regulatory interaction with FDA.
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use – Final	Provides FDA's interpretation of the existing regulatory definitions of minimal manipulation and homologous use. The guidance clarifies that these are distinct concepts and notes how to determine whether an HCT/P has been minimally manipulated or is intended for homologous use. The guidance also describes the compliance and enforcement policy that the FDA will use for HCT/Ps. For the first 36 months after issuance of the final guidance in November 2017, the FDA intends to exercise enforcement discretion for certain products that pose a low risk to public health so that sponsors will be able to have a dialogue with the agency and file the appropriate regulatory documentation.	Adipose tissue is considered to be a structural tissue for the purpose of the regulatory framework. This is relevant to determining the appropriate regulatory pathway for stem cells derived from adipose tissue, which in many applications will be regulated under both Sections 351 and 361 of the Public Health Service Act.
Evaluation of Devices Used with Regenerative Medicine Advanced Therapies – Draft	Provides a comprehensive resource to developers of devices used with RMATs. Topics covered include how the FDA will simplify and streamline its application of regulatory requirements for devices and cell-tissue combination products.	Under certain circumstances, a device that is used with an RMAT might be classified as a class III device or be limited to a specific intended use with only one type of cell.
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions -- Draft	Provides information about the expedited programs available to RMATs, including fast-track and breakthrough-therapy designations, and describes the FDA's considerations in implementing the new expedited program for RMATs. The guidance also describes an innovative program using cooperative development open to regenerative medicine products.	Multiple sites that manufacture a product using a common process may collaborate on clinical trials as part of a development program, which ultimately results in biologics licenses for each of the individual sites.

*The listed guidance documents can be accessed at:
www.fda/gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm58218.thm
RMAT denotes regenerative medicine advanced therapy
Source: Marks P, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. *N Engl J Med* 2018 378:954-959 (13).

8.6.1 Expediting the Development of New Therapies

The FDA has developed a process to expedite the development of new therapies. While the FDA has traditionally focused on ensuring the quality, safety, and efficacy of medical products, its mandate has expanded to include a role in accelerating the development of new therapies, particularly those aimed at treating serious or life-threatening conditions. Consequently, the expedited programs include fast track designation, priority review, accelerated approval, and designation as a breakthrough therapy.

The FDA reports that these programs have successfully expedited the development of new therapies. Additionally, the agency has emphasized its role in facilitating innovation while maintaining its approval standards, particularly in areas of unmet medical need and with emerging technologies, as outlined in the legislative initiative contained in the 21st Century Cures Act, enacted on December 13, 2016 (520).

To further advance therapeutic innovation in stem cell therapies and other HCT/Ps, the 21st Century Cures Act introduced an additional expedited program known as the Regenerative Medicine Advanced Therapy (RMAT) designation. This designation provides sponsors of qualified regenerative medicine products intended to treat serious or life-threatening conditions with benefits similar to those granted under the breakthrough therapy designation, provided that preliminary clinical evidence suggests the therapy addresses unmet medical needs.

The key distinction between RMAT and breakthrough therapy designation is that RMAT requires preliminary clinical proof of efficacy, whereas breakthrough designation requires preliminary evidence of a substantial improvement over existing therapy. Additionally, RMAT-designated products that receive accelerated approval may use a broader range of options to fulfill post-approval commitments, such as conducting traditional studies, maintaining patient

registries, or submitting other forms of objective real-world evidence. Multiple requests have been submitted for RMAT designation, with the FDA approving at least one-third of them.

8.6.2 Implementation of Comprehensive Framework

The FDA stated that it aims to apply a modernized approach to existing regulations and statutes, balancing the goal of promoting rapid development of innovative products for patients with medical needs while ensuring that such therapies remain both safe and effective. As part of this regulatory framework, the FDA articulated a risk-based compliance and enforcement policy. This policy allows developers of lower-risk products up to 36 months from November 16, 2017, to determine whether they need to submit an application for an investigational new drug or a marketing application in light of the newly published guidance documents. If such an application is required, developers are provided with time to prepare and submit it. However, the FDA intends to take enforcement actions in cases where it believes that unproven products may place patients at risk.

Working within the current regulatory framework, the FDA will use all available regulatory pathways and adopt new principles designed to make premarket evaluation of stem cell-based therapies more efficient. On a broader scale, the FDA will integrate new strategies to help small investigators and firms meet product approval standards through efficient and expedited pathways. To achieve this objective, the FDA will provide tools to encourage individual physicians or small groups of physicians to collaborate in the development of stem cell or other regenerative medicine products, ultimately enabling each participating physician or group to obtain a biologics license (Fig. 19).

9.0 Clinical Guidance

Key Question 10. What are the adverse consequences/harms of regenerative therapies?

Key Question 11. What are the precautions in perioperative management of patients receiving regenerative interventional techniques and antiplatelet and anticoagulant therapy.

Key Question 12. What are the best preventive and therapeutic strategies to improve outcomes when performing regenerative therapies?

9.1 Safety, Effectiveness, and Informed-Decision Making

Regenerative medicine remains a developing field that is not currently covered by medical insurance. At the time of this writing, there are no standardized protocols or treatments governed by the Centers for Medicare and Medicaid Services (CMS). Because of this, the physician–patient partnership must be emphasized more strongly than in most other procedures. Understanding the safety and effectiveness of treatments is essential to making informed decisions that best serve patients while advancing the field.

At its foundation, autologous sources of orthobiologics are inherently safe, as the injectate is obtained from and re-injected into the same patient. Autologous sources carry a very low risk of rejection, allergic reaction, or infection. Standard hygiene and sterilization protocols must always be followed when handling blood products. Most commercially available kits are closed systems, which further minimize the risk of contamination. Proper training in the handling of biologics (blood, bone marrow, adipose) is essential, as is ongoing protocol review. Physicians performing these procedures are expected to adhere to the same practice standards used for any injection procedure involving the joints or spine, maintaining sterile technique and image guidance. The most commonly reported adverse effects are mild and typically include injection-site pain, swelling, or stiffness that resolve over time and require only conservative management.

Numerous published studies discuss the effectiveness of orthobiologics. The 3 key variables influencing outcomes are dose, severity of the treated structure, and injection technique. These procedures must be performed by well-trained physicians under image guidance (fluoroscopy or ultrasound). Dosing and disease severity then become the primary determinants of efficacy. A review of the literature indicates that orthobiologic treatments show the greatest benefit for mild to moderate degeneration, tendinosis, and partial tears of ligaments and tendons. Quantitative analysis of the injectate is essential, as studies have demonstrated that therapeutic effectiveness depends on appropriate dosing. Generally, PRP concentrations exceeding 5 billion platelets and BMACs with more than 100 million total nucleated cells are recommended.

Interventional physicians presenting these treatment options to patients must be prepared to discuss the realistic potential of these procedures and manage patient expectations accordingly. Because these treatments remain an expensive, out-of-pocket expense for most patients, understanding their safety, effectiveness, and limitations is critical. A standard consent form for interventional procedures can serve as a foundation for informed consent. In our practice, additional language is included to explain the experimental nature of these treatments, as they are not FDA-approved for orthopedic conditions of the joints or spine. All treatment options are reviewed, and patient questions and concerns are fully addressed prior to proceeding with any orthobiologic procedure.

9.2 Office Set-up

When setting up an office for regenerative medicine, always prioritize decisions that optimize patient outcomes.

- Location: An ideal location is within a medical community near other practices, close to major freeways, and easily accessible for patients traveling from a distance. However, location is not critical, patients will travel for excellent care. For new practices, subleasing from an existing medical office can help reduce start-up costs. For existing practices adding regenerative medicine, utilize current office space but designate specific rooms, and ideally a separate waiting area, for regenerative medicine patients.
- Staffing: Dedicate one receptionist and one medical assistant to regenerative medicine. If adding regenerative medicine to an existing practice, obtain a separate phone number, create a Doing Business As (DBA), and use a distinct name for marketing. In the initial stages, the most important staff member is the receptionist. Invest in their training by having them observe consultations and procedures to

fully understand the process and accurately answer patient questions. How leads are handled is critical for converting inquiries into visits and procedures.

- Equipment and Supplies: A quantitative laboratory capable of providing cell counts for PRP and BMC samples is essential and often overlooked. Without knowing cell counts, dosing accuracy cannot be confirmed, and inadequate dosing can compromise outcomes.
- Ultrasound: Use ultrasound for both diagnostics and needle guidance. Proper training is crucial to develop proficiency. Ultrasound should become an extension of the physical exam for evaluating visible structures and ensuring accurate needle placement during procedures. Inaccurate delivery of regenerative products can lead to suboptimal results.
- Fluoroscopy: Use fluoroscopy for guidance during interosseous or intradiscal spine procedures. If a fluoroscope or lead-lined OR is not available in the office, partner with a local ambulatory surgery center and pay a facility fee per case. This arrangement is also suitable for procedures requiring anesthesia if in-office anesthesia is not feasible.
- Patient Registry: Maintain a patient registry to track treatment outcomes and share data with patients. Multiple regenerative registries are available; select one and use it consistently for all patients.
- Supplies: Supplies for regenerative medicine are similar to those used in pain management procedures and include local anesthetics, needles, syringes, ultrasound probe covers, and sterile prep materials. In addition to local anesthesia, nitrous gas is a suitable in-office option that avoids the requirements associated with intravenous (IV) anesthesia. Proper preoperative screening and intraoperative monitoring are essential for safe IV anesthesia administration.
- Electronic Medical Records: The choice of EMR depends on whether the practice is entirely out-of-pocket or mixed insurance and cash-based. If offering both, ensure proper advanced beneficiary notices and consent forms are used to confirm patient understanding that insurance will not be billed.
- Client Experience: Regenerative medicine differs from traditional pain management or "sick care." Patients seeking regenerative treatments are often proactive and have already decided to pursue these therapies, they are choosing whom to trust. Take the approach of a plastic surgery practice: be kind, take time during consultations, and clearly explain the rationale for each recommended procedure. Educate rather than sell. Avoid promotional tactics such as "book today and get $500 off"; instead, build trust through professionalism and transparency.

9.3 Contraindications

Absolute Contraindications – Regenerative medicine procedures, like conventional pain-relieving procedures, are elective. Injections should not be performed if any of the following conditions are present:

- Active Cancer
- Active infection
- Hemodynamically unstable or other disorder meeting hospitalization criteria
- Abnormally high numbers on baseline cell analysis could represent an undiagnosed cancer or active infection and need further work-up before reinjection.

Relative Contraindications – The risk versus benefit of treatment should be carefully considered in the following situations:

- Low baseline platelet counts (50-100k platelets/uL)
- Antiplatelet therapy, including NSAIDs
- Immunotherapy disease-modifying antirheumatic drugs (DMARDs)
- Low PRP or BMC numbers on post-processing cell analysis, as injecting a suboptimal dose is less likely to be effective.
- Advanced conditions have a lower probability of efficacy due to a lower baseline substrate.
- Bony growths, such as osteophytes, are sources of pain/tear.
- Significant loss of range of motion, causing significant functional limitations, as range of motion tends not to improve with treatment.
- Unhealthy patients with poor protoplasm, such as those with metabolic syndrome, organ failure, or home oxygen use, have reduced regenerative capacity.
- Inability to participate in a proper rehabilitation program post-procedure.

9.4 Pre, Intra, and Post Procedural Considerations

9.4.1 Pre-Procedure

Orthobiologic treatment protocols continue to evolve. As with any intervention, identifying appropriate candidates and target diagnoses is essential. Maximizing the benefit of orthobiologics requires accurate

identification of the anatomical structures responsible for symptoms. Patients with multiple systemic or autoimmune disorders may not be suitable candidates. Studies have shown that PRP is beneficial for soft tissue injuries and mild degenerative conditions, while BMAC is more effective for advanced cases. Once the treatment plan is established, target structures and concentration volumes should be determined in advance.

Active infection or cancer, thrombocytopenia, NSAID or immunotherapy use, prior surgery at the treatment site, and imaging findings should be reviewed as relative contraindications. A complete blood count is recommended for patients with a history of cancer, infection, or thrombocytopenia before treatment. Discontinuation of NSAIDs and immunotherapy 7–10 days prior to and for 2 weeks following the procedure is advised to optimize results. Adequate hydration for 2–3 days before the procedure is recommended. Supplements may also be considered before and after the procedure to support recovery.

9.4.2 Intra-Procedure

For PRP, venous blood should be drawn using a large-bore needle (18–20 G) to minimize cellular damage. Double centrifugation producing over 10 billion platelets yields optimal results. Bone marrow aspiration is typically performed at the posterior superior iliac spine (PSIS). After concentration, a total nucleated cell count above 1.5 billion is the goal.

The needle approach should be carefully planned, accounting for anatomical variations and nearby neurovascular structures. Image guidance (ultrasound or fluoroscopy) is required for precise placement of the orthobiologic material. IV conscious sedation or inhaled nitrous oxide may be used for comfort. The treatment area should be prepared and draped in a sterile manner. IV antibiotics are recommended for intradiscal and intraosseous procedures. Vital signs must be continuously monitored according to American Society of Anesthesiologists (ASA) guidelines during the procedure to ensure patient safety.

9.4.3 Post-Procedure

Post-procedural care includes monitoring for bleeding or infection and maintaining hydration. Acceptable post-injection medications include gabapentinoids, acetaminophen, muscle relaxants, and opioids as alternatives to NSAIDs. Cryotherapy can be applied to the treatment site for the first 24 hours, followed by heat therapy thereafter. Cryotherapy may also be continued at the bone marrow aspiration site. Patients should avoid overuse of the treated area.

Symptoms often intensify during the first 7–10 days after injection due to the inflammatory healing response but typically return to baseline within a few weeks. Range of motion and daily activities are encouraged until the 4-week follow-up. From weeks 4–6, patients should begin a home exercise program at approximately 50% of normal intensity using isometric exercises, increasing activity gradually based on tolerance and avoiding prolonged soreness. After 6 weeks, most activity restrictions are lifted if symptoms remain controlled. Noticeable improvement typically occurs between weeks 4–6, with continued progress for several months. Follow-up evaluation is generally performed at 3 months post-injection.

9.5 Post-Orthobiologic Rehabilitation

Tissue healing follows a predictable cascade initiated by an external trigger, either an injury or an orthobiologic treatment. Although there is considerable variability in published rehabilitation protocols (339), the standard approach aligns with the 4 overlapping phases of tissue healing (521):

Stage 1: Hemostasis
Stage 2: Acute inflammatory phase
Stage 3: Proliferative or repair phase
Stage 4: Remodeling phase

During rehabilitation, it is important to recognize that optimal loading can improve a tissue's mechanical properties by enhancing fiber alignment through progressive, therapeutic stress (522). Because the rate and strength of healing are tissue-specific, so too is optimal loading. Insufficient loading may weaken tissue and impair mobility, while excessive loading may damage newly formed tissue; moderate loading, in contrast, supports the repair process.

The physiologic timeframe for tissue loading and protection is outlined in Table 21 (521). During the hemostatic and inflammatory stages, limited or protected weight-bearing facilitates cross-link formation, while gentle motion prevents stiffness. Pain typically decreases as healing progresses to the proliferative phase (weeks 3–6), during which light concentric and later eccentric loading can aid recovery. Adjunctive techniques, including soft tissue mobilization and extracorporeal shockwave therapy, may be beneficial. From weeks 6–12, the remodeling phase features increased tensile strength as type 3 collagen is replaced by a more organized matrix.

Table 21. *Tissue-specific loading and healing time.*

Tissue	Healing Capacity Vacularity	Force to Facilitate Healing	Tissue Healing Time	Loading Protection
Muscle	Good, abundant	Contractile Loading Isometric-> Concentric-> Eccentric muscle	6-8 wk	ROM parameters, SubMax Isometrics-> Max Isometrics-> Concentrics-> Eccentrics-> Ballistic progressions
Tendon	Fair, less	Contractile Loading Isometric-> Concentric-> Eccentric	8-12 wk	ROM parameters, SubMax Isometrics-> Max Isometrics-> Concentrics-> Eccentrics-> Ballistic progressions
Ligament	Less, Diminished	Tension Controlled fiber Tension in line of stress	7-14 wk	Bracing with protected ROM parameters
Cartilage Labrum Intervertebral Disc	Limited/absent	Cyclical Compression, Decompression & Shear Imbibing pumping effect; controlled	6-12 wk	Bracing, Unloading, progressing weight bearing, Aquatics, Stationary Bike, weight bearing loading and controlled torsional stress
Subchondral Bone/Bone		Controlled Weight Bearing	8-12 wk	Weight Bearing Status, Unloading

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Toward the end of this stage, functional exercises and gradual return to full activity may occur (521). However, individual variations of 4–8 weeks are common, depending on pathology, comorbidities, biomechanics, activity level, and tissue quality.

9.6 Adverse Reactions and Complications

Orthobiologic injections are among the safest orthopedic procedures due to their typically autologous nature, minimally invasive technique, and lack of systemic adverse effects. Nonetheless, patients should be informed about possible risks, benefits, and indications.

The most common adverse effect is transient postprocedural pain (523), resulting from the localized inflammatory response that drives the therapeutic effect. A 2024 review of adverse events associated with PRP primarily identified isolated case reports of local infection following musculoskeletal PRP injection. Additional reports included one allergic reaction to calcium citrate and 2 cases of persistent synovitis (524).

Because intervertebral discs are avascular, intradiscal injections carry a higher risk of infection. Discitis has been reported following intradiscal bone marrow concentrate, adipose, and leukocyte-poor PRP injections (525). A meta-analysis by Peng et al (420) evaluating intradiscal PRP injections for discogenic low back pain found no significant adverse events across 6 studies, including 3 randomized controlled trials and 3 prospective single-arm trials.

To reduce the risk of discitis, recommendations include using leukocyte-rich PRP, administering intradiscal antibiotics (525), applying a double-needle technique, and sterilizing the field twice with chlorhexidine (526).

Although theoretical concerns exist regarding neoplasm formation, a multicenter study of over 2,300 patients treated with MSCs derived from bone marrow and adipose tissue for musculoskeletal disorders showed a lower incidence of neoplasms compared to the general population (523).

10.0 Antithrombotic Implications

10.1 Risks in Regenerative Medicine

Bone marrow aspirations and intra-articular or soft tissue injections are associated with low bleeding risk, whereas central nervous system or meningeal-related injections carry a higher bleeding risk. ASIPP conducted a comprehensive review with a literature search (44,45) to analyze multiple guidelines and produce recommendations specific to interventional techniques and associated bleeding risks. These recommendations are influenced by factors including patient-specific risk profiles and the judgment of the managing physician (44,45,527–532). Thromboembolic events must also be considered, as any interventional procedure carries some bleeding risk. Clinical correlation with the patient's medical history, social history, and individual risk factors is essential.

10.2 Effects of Antithrombotic Therapy on PRP and Stem Cell Effectiveness

The coagulation cascade is critical to platelet function, and disruption of platelet surfaces or premature activation may reduce clinical efficacy (532). With the increasing use of MSC technology in regenerative medicine, cell viability must also be considered in the context of antithrombotic therapy. Studies show that even low-dose heparin can negatively affect ex vivo MSC growth and differentiation potential, highlighting the importance of evaluating bone marrow in patients receiving heparin, particularly when ex vivo expansion of human mesenchymal stem cells (hMSCs) is planned (533).

PRP use is rising due to its potential to promote ligament and tendon healing and serve as a non-surgical alternative. Many candidates for PRP therapy, however, are on anticoagulants or antiplatelet drugs. While anticoagulants are necessary during PRP processing to prevent premature activation, systemic antithrombotic agents influence platelet stability and likely reduce PRP efficacy, necessitating discontinuation prior to injection therapy (534). PRP enhances cell proliferation, collagen synthesis, angiogenesis, and revascularization, supporting tissue regeneration. Sutherland et al (534) demonstrated the effectiveness of autologous MSCs in regenerative medicine using sheep models for tissue-engineered heart valve reconstruction.

The regenerative effect of PRP relies on localized release of bioactive factors such as cytokines and growth factors, which are activated and aggregated at the injury site. Platelet characteristics, particularly their activation and aggregation potential, are therefore critical (535). NSAIDs inhibit platelet activation, reduce alpha granule storage, and impair aggregation. This results in lower-quality autologous PRP and may negatively affect healing outcomes. Studies have shown that NSAID exposure significantly inhibits platelet function, regardless of the drug type, duration, or blood processing method used for PRP preparation (535). Cyclooxygenase inhibition by NSAIDs impedes platelet activation and release of growth factors, including TGF-α and platelet factor 4, confirming that PRP produced after NSAID use may be suboptimal.

While NSAIDs remain important for pain control post-injury, their effect on bone healing is debated. Animal studies demonstrate mixed outcomes, and clinicians are cautioned that the absence of definitive evidence does not indicate safety, emphasizing that NSAIDs should be avoided in high-risk patients (536).

Ramsook and Danesh (532) discussed PRP use in the context of antithrombotic therapy, emphasizing that disruption of the coagulation cascade may result in prematurely activated platelets and reduced efficacy. They recommend discontinuing antithrombotic agents within an appropriate timeframe prior to injection therapy. Overall, principles regarding antithrombotic and anticoagulant management are consistent with those used in other interventional techniques.

There remains limited literature regarding the safety, efficacy, and timing of PRP injections in patients on antithrombotic therapy. The integrity of platelet membranes is essential for proper release of growth factors and bioproteins, which underpins PRP efficacy. Antithrombotic agents that destabilize platelets reduce PRP effectiveness, highlighting the need for proper discontinuation protocols. Future research may provide clearer guidance for PRP and stem cell therapy in these patients.

10.3 Safe and Efficient Administration of Regenerative Medicine in Anticoagulated Patients

The use of regenerative medicine interventions in patients receiving anticoagulant and antiplatelet therapy is increasing (44). This trend necessitates a multidisciplinary approach to balance the importance of anticoagulation with the requirements of interventional procedures, including timing, discontinuation, or temporary interruption of therapy (44). Anticoagulants and antiplatelet agents are commonly prescribed to reduce thromboembolic risk in patients with conditions such as angina, atherosclerosis, atrial fibrillation, cerebrovascular accidents, ischemic heart disease, myocardial infarction, pulmonary embolism, and peripheral vascular disease. Treatment strategies may include continuation of oral anticoagu-

lants, switching to alternate agents, adding antiplatelet therapy, performing left atrial appendage closure, or combining these approaches (537).

The 2024 ASIPP updated guidelines provide consensus-based recommendations on perioperative management of antiplatelet and anticoagulant therapy in patients undergoing interventional procedures. These guidelines are based on best evidence synthesis, review of bleeding risks, practice patterns, and perioperative management strategies (44). Risk stratification of interventional procedures incorporates: anatomic factors, procedural factors, bleeding risk factors, anticoagulant/antiplatelet-related risks, and medical or physiological risk factors. Table 22 summarizes factors associated with increased bleeding risk (538).

10.4 Determination of Timing of Anticoagulant Interruption

The timing of anticoagulant use and its interruption is a critical consideration and varies among specialties and authors. Table 23 presents sample recommended preoperative withholding times for oral antiplatelet and anticoagulant drugs as reported in the literature (539). Figure 20 illustrates an algorithm for anticoagulant and antiplatelet discontinuation in patients undergoing interventional procedures.

Figure 21 depicts recommended perioperative withholding times for antiplatelet or anticoagulant drugs, reflecting recommendations from various authorities. For high-risk procedures, aspirin, clopidogrel (Plavix), and prasugrel (Effient) are discontinued 6 days before the procedure and can be resumed the following day. Ticagrelor (Brilinta) is stopped 5 days before and resumed the day after the procedure. For intermediate or moderate-risk procedures, aspirin is discontinued 3 days prior, clopidogrel (Plavix) 5 days, prasugrel (Effient) 5 days, and ticagrelor (Brilinta) 3 days. Recommendations for low-risk procedures are variable; drugs may either be continued or withheld based on clinical judgment and procedural risk.

Table 22. *Factors associated with increased bleeding risk.*

Need for oral anticoagulation in addition to dual antiplatelet therapy
Advanced age (older than 75 years)
Frailty
Anemia with hemoglobin < 110 g/L
Chronic renal failure (creatinine clearance < 40 mL/min)
Low body weight (<60 kg)
Hospitalization for bleeding within past year
Previous stroke/intracranial bleed
Regular need for NSAIDs or prednisone

NSAIDs: nonsteroidal anti-inflammatory drugs
Source: Mehta SR, Bainey KR, Cantor WJ et al; members of the Secondary Panel. 2018 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. *Can J Cardiol* 2018; 34:214-233 (538).

Table 23. *Recommended preoperative withholding times of oral antiplatelet and anticoagulant drugs.*

Drug	Half-life	Time to withhold prior to		Time to restart after	
		Minor surgery	Major surgery	Minor surgery	Major surgery
Warfarin (Coumadin)	20–60 h	3–5 days*	3–5 days	24 h, overlapping therapy with heparin	48–72 h; overlapping therapy with heparin
Apixaban (Eliquis)	8–15 h	24 h**	48 h**	24 h	24–48 h
Rivaroxaban (Xarelto)	5–9 h (Elderly: 11–13 h)	24 h**	48 h**	24 h	24–48 h
Edoxaban (Savaysa, Lixiana)	10–14 h	24 h**	48 h**	24 h	24–48 h
Betrixaban (Bevyxxa)	19–27 h	≥ 4 days	≥4 days	24 h	24–48 h
Dabigatran (Pradaxa)	12–17 h	CrCl > 50 mL: 24 h CrCl < 50 mL: 72 h	CrCl > 50 mL: 72 h CrCl < 50 mL: 120 h	24 h	24–48 h
Aspirin	7–10 days	usually continued	usually continued	usually continued	usually continued
Clopidgrel (Plavix)	7–10 days	5–7 days	5–7 days	24 h	24–48 h
Prasugrel (Effient)	7–10 days	5–7 days	5–7 days	24 h	24–48 h
Ticagrelor (Brilinta)	5–7 days	3–5 days	3–5 days	24 h	24–48 h

*In some cases, continued drug administration is feasible
**In case of impaired renal function, withholding interval should be prolonged and/or drug level should be evaluated by laboratory tests
CrCl: creatinine clearance
Adapted and modified: Moster M, Bolliger D. Perioperative guidelines on antiplatelet and anticoagulant agents: 2022 update. *Curr Anesthiol Rep* 2022; 12:286-296 (372).

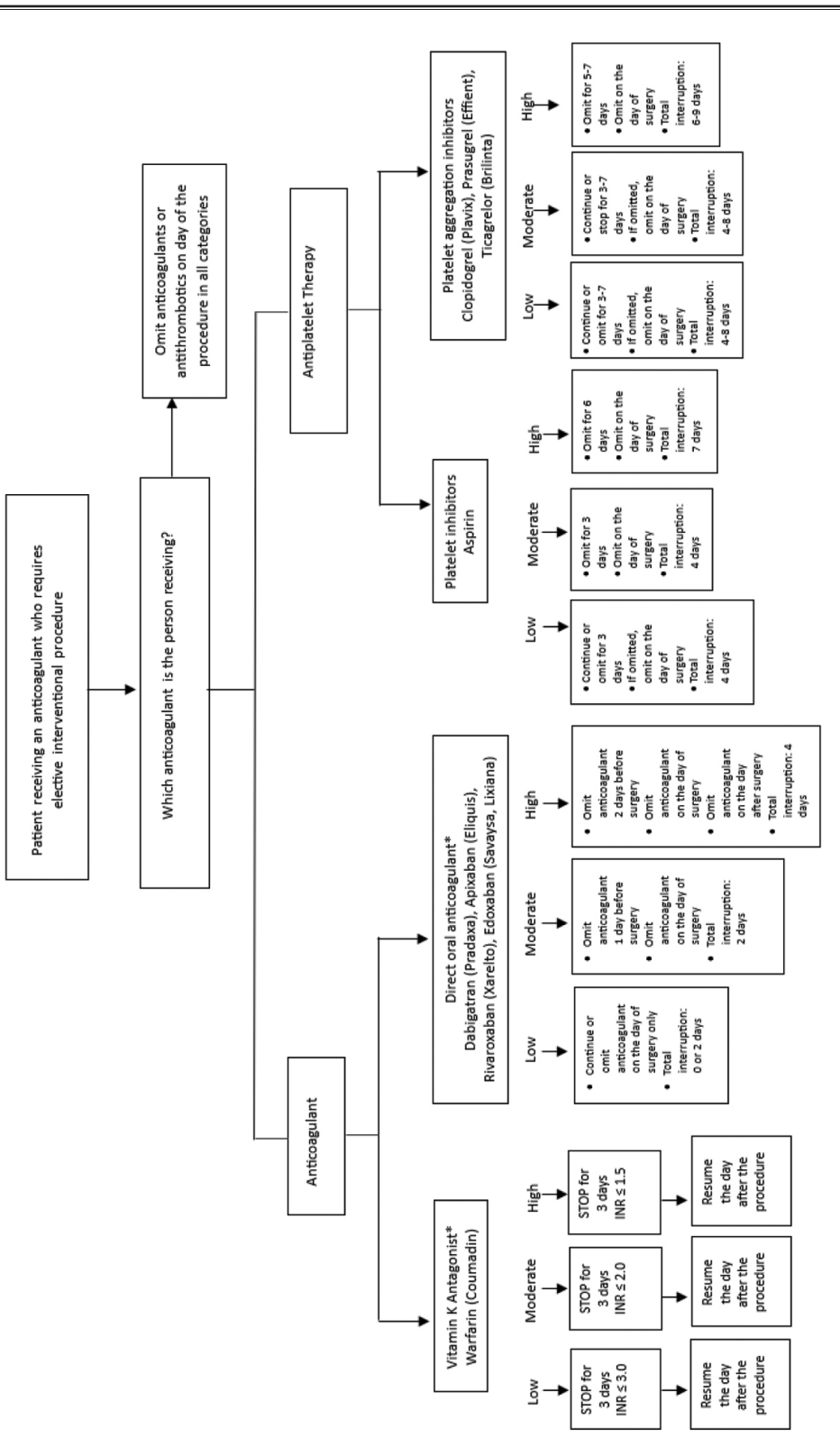
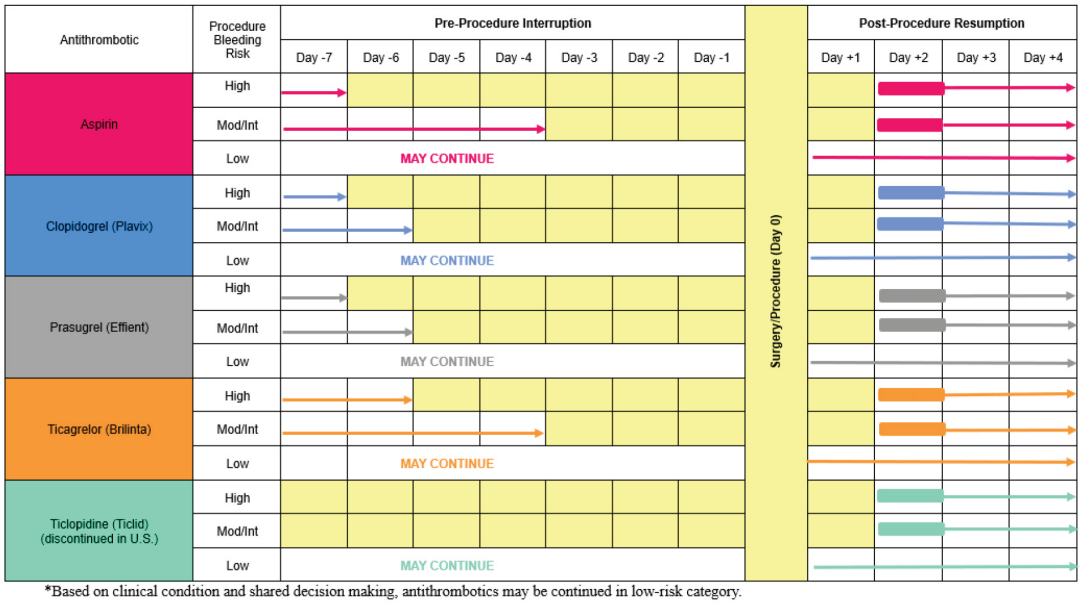


Fig. 20. *An algorithm for anticoagulant and antiplatelet discontinuation in individuals undergoing interventional procedures.*

**Anticoagulants:*

- *Vitamin K antagonists include warfarin (Coumadin)*
- *Direct oral anticoagulants (DOACs) include dabigatran (Pradaxa), apixaban (Eliquis), rivaroxaban (Xarelto), and edoxaban (Savaysa, Lixiana)*
- *Platelet inhibitors include aspirin*
- *Platelet aggregation inhibitors include clopidogrel (Plavix), Prasugrel (Effient), and Ticagrelor (Brilinta)*

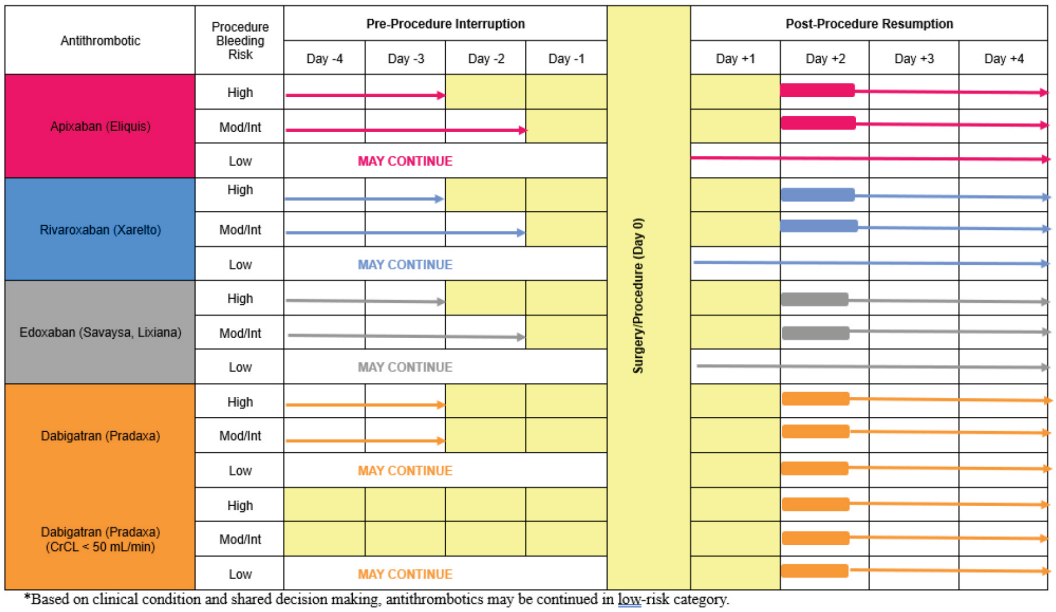


*Based on clinical condition and shared decision making, antithrombotics may be continued in low-risk category.

No antithrombotic administered that day

*DOAC can be resumed ~24 hours after low/moderate-bleed-risk procedures, and 48-72 hours after high-bleed-risk procedures. In selected patients at high risk for VTE, low-dose anticoagulants (i.e., enoxaparin, 40 mg daily or dalteparin, 5,000 IU daily) can be given for the first 48-72 hours post-procedure.

Fig. 21. *Perioperative management of antiplatelet or anticoagulant drugs for interventional procedures.*



*Based on clinical condition and shared decision making, antithrombotics may be continued in low-risk category.

CrCl = creatinine clearance

No DOAC administered that day

*DOAC can be resumed ~24 hours after low/moderate-bleed-risk procedures, and 48-72 hours after high-bleed-risk procedures. In selected patients at high risk for VTE, low-dose anticoagulants (i.e., enoxaparin, 40 mg daily or dalteparin, 5,000 IU daily) can be given for the first 48-72 hours post-procedure.

Fig. 22. *Perioperative management of interventional techniques in patients on direct oral anticoagulants (DOACs).*

Figure 22 presents perioperative management of patients receiving direct oral anticoagulants during interventional procedures. For high-risk patients, direct oral anticoagulants are interrupted 2 days before, on the day of, and one day following the procedure, totaling 4 days, except in patients with creatinine clearance ≤ 50 mL/min. In such cases, dabigatran (Pradaxa) is stopped for 4 days and resumed on day two, totaling 6 days of cessation. For intermediate or moderate-risk patients, preprocedural cessation is 2 days, including the day before and the day of the procedure, with resumption the next day. Dabigatran in this category is interrupted for 2 days with resumption on the first day post-procedure, totaling 3 days. For low-risk patients, cessation is generally unnecessary, but adjustments may be made depending on individual variables, following the intermediate-risk recommendations if indicated.

Regarding warfarin (Coumadin), Douketis et al (540,541) recommend continuation for minimal bleeding risk. For low to moderate bleeding risk, warfarin is withheld for 5 days with bridging, though the guidance notes limited benefit of bridging. For interventional procedures, a 1–3 day interruption is recommended to achieve an optimal INR ≤ 3.0 for low-risk procedures, 2–3 days with INR ≤ 2.0 for intermediate-risk procedures, and 3–5 days with INR ≤ 1.5 for high-risk procedures. Low molecular weight heparin bridging may be considered for high-risk procedures such as SCS and intrathecal implantable device placement. Bridging may be managed by a cardiologist or, if recommended, by the interventional pain physician.

Based on these considerations, ASIPP guidance has developed an algorithmic approach for interventional procedures in patients on anticoagulant or antiplatelet therapy, as shown in Figure 20.

Table 24. *ASIPP guidelines for antithrombotic medication management and interventional techniques.*

MEDICATION	Time to Wait After Last Dose of Medication Before Interventional Techniques Are Performed			Timing of Therapy Restoration or Restarting
	LOW RISK PROCEDURES	MODERATE OR INTERMEDIATE RISK PROCEDURES	HIGH-RISK PROCEDURES	
	• Trigger point and intramuscular injections • Peripheral nerve blocks • Sacroiliac joint injections • All facet joint interventions (intra-articular injections, medial branch and L5 dorsal ramus nerve blocks and radiofrequency neurotomy) • Intraarticular injections of extremities • Pocket revision and implantable pulse generator/intrathecal pump replacement • Peripheral nerve stimulation trial and implantation of extremities and other superficial nerves • Lumbar transforaminal epidural injections at L3, L4, L5, and S1 • Ganglion impar blocks • Sacroiliac joint nerve radiofrequency • Trigeminal branch nerve blocks (mandibular, maxillary, and other branches)	• Caudal epidural injections • Caudal epidural adhesiolysis • Lumbar interlaminar epidural at L5, S1 • Cervical, thoracic, and lumbar transforaminal at L1 and L2 • Peripheral nerve stimulation trial and implantation of lumbar medial branches	• Cervical, thoracic, and lumbar (above L5) interlaminar epidurals • Peripheral nerve stimulation trial and implantation of thoracic and cervical medial branches • Trigeminal ganglion, ophthalmic division, and sphenopalatine ganglion blocks • Discography and intradiscal procedures • Dorsal column and dorsal root ganglion stimulator trial and implantation • Intrathecal catheter and pump implant • Vertebral augmentation • Percutaneous and endoscopic disc decompression procedures • Minimally invasive lumbar decompression (MILD) • Trigeminal and cranial nerve blocks and stimulation • Sympathetic blocks (stellate ganglion, thoracic sympathetic, splanchnic, celiac plexus, lumbar sympathetic, hypogastric plexus) • Percutaneous adhesiolysis with interlaminar or transforaminal approach (cervical, thoracic, and lumbar) • Intervertebral spinous prosthesis including lateral fusion • SI joint fusion • Intracept procedure	

Table 24 cont. *ASIPP guidelines for antithrombotic medication management and interventional techniques.*

MEDICATION	Time to Wait After Last Dose of Medication Before Interventional Techniques Are Performed			Timing of Therapy Restoration or Restarting
	LOW RISK PROCEDURES	MODERATE OR INTERMEDIATE RISK PROCEDURES	HIGH-RISK PROCEDURES	
	• Trigger point and intramuscular injections • Peripheral nerve blocks • Sacroiliac joint injections • All facet joint interventions (intra-articular injections, medial branch and L5 dorsal ramus nerve blocks and radiofrequency neurotomy) • Intraarticular injections of extremities • Pocket revision and implantable pulse generator/intrathecal pump replacement • Peripheral nerve stimulation trial and implantation of extremities and other superficial nerves • Lumbar transforaminal epidural injections at L3, L4, L5, and S1 • Ganglion impar blocks • Sacroiliac joint nerve radiofrequency • Trigeminal branch nerve blocks (mandibular, maxillary, and other branches)	• Caudal epidural injections • Caudal epidural adhesiolysis • Lumbar interlaminar epidural at L5, S1 • Cervical, thoracic, and lumbar transforaminal at L1 and L2 • Peripheral nerve stimulation trial and implantation of lumbar medial branches	• Cervical, thoracic, and lumbar (above L5) interlaminar epidurals • Peripheral nerve stimulation trial and implantation of thoracic and cervical medial branches • Trigeminal ganglion, ophthalmic division, and sphenopalatine ganglion blocks • Discography and intradiscal procedures • Dorsal column and dorsal root ganglion stimulator trial and implantation • Intrathecal catheter and pump implant • Vertebral augmentation • Percutaneous and endoscopic disc decompression procedures • Minimally invasive lumbar decompression (MILD) • Trigeminal and cranial nerve blocks and stimulation • Sympathetic blocks (stellate ganglion, thoracic sympathetic, splanchnic, celiac plexus, lumbar sympathetic, hypogastric plexus) • Percutaneous adhesiolysis with interlaminar or transforaminal approach (cervical, thoracic, and lumbar) • Intervertebral spinous prosthesis including lateral fusion • SI joint fusion • Intracept procedure	
NSAIDS (COX 1) (COX 2)	May continue or stop 1-10 days due to lack of protective effect	May continue or stop 1-10 days due to lack of protective effect	May continue or stop 1-10 days due to lack of protective effect	24 hours
THC/CBD	May continue or stop 1-10 days	May continue or stop 1-10 days	Stop for 5 days	24 hours
Garlic	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Vitamin E	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Fish Oil	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Aspirin				
Low-Dose Aspirin	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
High Dose Aspirin	Continue or may stop for 3 days	Continue or may stop for 3 days	Stop for 6 days	24 hours
Antiplatelet Agents (Phosphodiesterase Inhibitors)				
Dipyridamole (Persantine)	May continue	May continue	May continue or stop for 2 days	12 hours
Cilostazol (Pletal)	May continue	May continue	May continue or stop for 2 days	12 hours
Aggrenox (dipyridamole plus aspirin)	May continue	May continue	Stop for 6 days	24 hours
Platelet Aggregation Inhibitors				

Table 24 cont. *ASIPP guidelines for antithrombotic medication management and interventional techniques.*

MEDICATION	Time to Wait After Last Dose of Medication Before Interventional Techniques Are Performed			Timing of Therapy Restoration or Restarting
	LOW RISK PROCEDURES	MODERATE OR INTERMEDIATE RISK PROCEDURES	HIGH-RISK PROCEDURES	
Clopidogrel (Plavix)	May continue	May continue or stop for 5 days	Stop for 6 days	12 hours
Prasugrel (Effient)	May continue	May continue or stop for 5 days	Stop for 6 days	24 hours
Ticagrelor (Brilinta)	May continue	May continue or stop for 3 days	Stop for 5 days	24 hours
Vitamin K Antagonists				
Warfarin	May continue or stop for 1-2 days INR ≤ 3.0	May continue or stop for 2-3 days INR ≤ 2.0	Stop for 3-5 days INR ≤ 1.5	12-24 hours
Direct Oral Anticoagulants (DOACs)				
Dabigatran (Pradaxa)	May continue or stop for 1 day	Stop for 2 days	Stop for 2 days	24 hours
Dabigatran (Pradaxa) (CrCl ≤ 50 ml/min)	May continue or stop for 1 day	Stop for 3-4 days	Stop for 3-4 days	24 hours
Apixaban (Eliquis)	May continue or stop for 1 day	Stop for 1 day	Stop for 2 days	24 hours
Rivaroxaban (Xarelto)	May continue or stop for 1 day	Stop for 1 day	Stop for 2 days	24 hours
Edoxaban (Savaysa, Lixiana)	May continue or stop for 1 day	Stop for 1 day	Stop for 2 days	24 hours
Heparins				
Heparin (treatment) - IV	Discontinue for 4 hours	Discontinue for 4 hours	Discontinue for 4 hours	24 hours
Heparin (treatment) - SC	Discontinue for 6 hours	Discontinue for 6 hours	Discontinue for 24 hours	24 hours
Low Molecular Weight Heparin	Discontinue for 24 hours	Discontinue for 24 hours	Discontinue for 24 hours	24 hours

Adapted and modified from: Manchikanti L, Sanapati MR, Nampiaparampil D, et al. Perioperative management of antiplatelet and anticoagulant therapy in patients undergoing interventional techniques: 2024 updated guidelines from the American Society of Interventional Pain Physicians (ASIPP). *Pain Physician* 2024; 27:S1-S94 (369).

10.5 Guidelines for Managing Anticoagulant and Antiplatelet Therapy During Interventional Techniques

ASIPP guidelines and recommendations are based on a comprehensive literature review of thromboembolic risk, bleeding risk, anatomical considerations, procedural factors, and medical or physiological status. Prior guidelines for interventional pain management, general surgery, endoscopy, and ophthalmic surgery from multiple organizations were also reviewed. Table 24 presents recommended management of antiplatelet and anticoagulant medications for interventional procedures (44), while Table 25 provides a procedural checklist for managing anticoagulant and antiplatelet therapy during interventional techniques.

Table 25. *Procedural checklist for managing anticoagulant and antiplatelet therapy during interventional techniques.*

PROCEDURE:
1.0 Patient evaluation and Identification of Risk Factors ❑ 1.1 Age ❑ 1.2 Diabetes ❑ 1.3 Bleeding disorders ❑ 1.4 Hypertension ❑ 1.5 Obesity ❑ 1.6 Low body weight ❑ 1.7 Renal disease ❑ 1.8 Low creatinine clearance
2.0 Identification of Anticoagulant or Antithrombotic Medication ❑ 2.1 Aspirin Use: • Primary Prophylaxis: Absence of established cardiovascular disease or risk factor • Secondary Prophylaxis: Presence of cardiovascular or cerebrovascular disease ❑ 2.2 Antiplatelets • Clopidogrel (Plavix) • Prasugrel (Effient) • Ticagrelor (Brilinta) ❑ 2.3 Direct oral anticoagulants (DOACs) • Dabigatran (Pradaxa) • Apixaban (Eliquis) • Rivaroxaban (Xarelto) • Edoxaban (Savaysa, Lixiana) ❑ 2.4 Warfarin (Coumadin) ❑ 2.5 Identification of over-the-counter drugs influencing thrombolysis: • Garlic • Vitamin E ❑ 2.6 Fish Oil • Primary Prophylaxis: Absence of established cardiovascular disease or risk factor • Secondary Prophylaxis: Presence of cardiovascular or cerebrovascular disease ❑ 2.7 SSRIs • Citalopram (Celexa) • Fluoxetine (Prozac) • Escitalopram (Lexapro) • Paroxetine (Paxil) • Sertraline (Zoloft) ❑ 2.8 NSAIDs
❑ 3.0 Risk Stratification and Recommendations • Low risk • Moderate or intermediate risk • High risk
❑ 4.0 Informed Decision Making
❑ 5.0 Restarting of Drugs
❑ 6.0 Postoperative Monitoring

11.0 Guidance for Safe and Effective Use of Biologics

The current body of evidence on the use of orthobiologics for the spine remains limited. Variations in the extent and duration of pathology, types of biologic products, procedural techniques, and outcome measures make it challenging to draw definitive recommendations from the literature. The lack of standardization in methodology and analysis hinders the ability to reproduce study models or make firm conclusions. As factors influencing healing and regeneration remain incompletely understood, clinicians continue to experiment with new combinations, further contributing to heterogeneity in composition, techniques, and outcomes (25,416,542).

In general, clinical studies indicate that orthobiologic therapies for low back pain are well-tolerated, with few reported side effects. Evidence suggests that orthobiologic injections may offer meaningful pain relief and improved function for patients with degenerative disc disease and related spinal conditions. However, the predictability of structural repair remains inconsistent across studies.

The high cost of orthobiologic injections and lack of insurance coverage continue to be significant barriers to widespread access and adoption, limiting availability for many patients. This situation may change as more robust data on the safety and long-term effectiveness of biologics, compared with corticosteroids, become available. Large-scale randomized controlled trials are essential to determine whether orthobiologic therapies provide consistent, durable results for low back pain and to identify the conditions under which they are most effective.

12.0 Future Perspective

Over the past decade, the field of orthobiologics has experienced substantial growth, and its future holds significant potential for expansion in both evidence-based applications and clinical utilization (1-34,543-546). Continued progress is expected to refine treatment indications and contraindications, optimize cellular dosing, and facilitate the development of combination therapies that integrate orthobiologics with other interventional techniques. Advancements in bioengineering and tissue engineering are anticipated to enhance product lines and drive innovation throughout the field.

Clinical data generally demonstrate higher efficacy in treating vascularized structures such as bone, tendon, and ligament. One of the greatest long-term challenges, however, lies in addressing less vascularized tissues such as fibrocartilage and intervertebral discs. Future success will rely on a comprehensive understanding of the genetic, anatomical, biomechanical, environmental, and lifestyle factors that influence treatment outcomes. This insight will support more deliberate and personalized application of orthobiologics, ultimately improving patient outcomes.

Collaboration among key professional societies will be essential for advancing the field. Such partnerships are expected to play a pivotal role in developing standards of care, best practice guidelines, compliance policies, and certification programs that ensure high-quality treatment at the point of care.

Biologic therapies hold significant potential to relieve pain, enhance patients' quality of life, and regenerate damaged tissues, potentially reversing age-related degeneration or spinal injuries. While challenges remain in ensuring long-term safety, efficacy, and accessibility, addressing these hurdles could enable orthobiologics to transform spine care, offering minimally invasive regenerative solutions that reduce the need for surgical interventions and provide durable patient benefit.

13.0 Recommendations and Statements

1. What are the available regenerative medicine therapies in the United States?
   Answer: Available regenerative medicine therapies include PRP and BMC when obtained with FDA-cleared devices.

   Evidence Level: High; Consensus-Based Clinical Recommendation: High

2. What are the potential regenerative medicine modalities are available in other countries but not the United States?
   Answer: Multiple therapies are not currently available due to FDA regulations in the United States. In other countries, multiple therapies are available, including adipose stem cells including stromal vascular fraction (SVF), autologous, allogenic, or stored stem cells, stem cells derived from umbilical cord and exosomes. There is no clear guidance on micronized fat and it is used by some in the field.

   Evidence Level: High; Consensus-Based Clinical Recommendation: High

3. What are the recognized risks of unapproved stem cell treatments.
   Answer: There are rare, but significant potential risks associated with unapproved stem cell treatments, including blindness, infections (like human immunodeficiency virus, hepatitis, or bacterial infections), thrombosis, tumor formation, neurological complications, and even death.

   Evidence Level: Moderate; Consensus-Based Clinical Recommendation: High

4. Defining Functional Spine Unit.
   Answer: A functional spinal unit (FSU), also known as spinal motion segment, or articular tide, is the smallest physiological unit of the spine that exhibits the same biomechanical properties of the entire spine. Each FSU is a 3-joint complex and is responsible for coordinated movement protecting neural structures and providing a stable base for the body. A FSU consists of 2 adjacent vertebrae, intervertebral disc, facet joints, ligaments, and muscles. The concept of FSU is crucial for understanding spine health and dysfunction related to degeneration, injury, diagnosis and treatment.
   Functional spine unit is utilized in managing back pain in regenerative medicine, in application of therapies in contrast to precision diagnosis and therapy with the single structure, as advocated in interventional pain management.
   While this approach appears to be appropriate considering that regenerative medicine therapies are not bound by LCDs and medical policies, functional spine unit may provide better results; however, there is no significant evidence at the present time.

   Evidence Level: Very Low; Consensus-Based Clinical Recommendation: Low

5. What are the identified risks of regenerative medicine therapies?
   Answer: Regenerative medicine therapies are similar to interventional techniques with low risk; however, severe complications can occur including infection, specifically, discitis, epidural hematoma, and abscess, superficial infections, allergies, neurological complications, tumor formation and death.
   Overall risk of interventional procedures has been considered by some as higher because of the steroid-based injections with chondrotoxicity, tenotoxicity, neurotoxicity, and multiple systematic toxicities. These toxicities are absent with PRP and BMC.

   Evidence Level: High; Consensus-Based Clinical Recommendation: High

6. Platelet Rich Plasma (PRP): Quality and Standards
   Answer: Key issues concerning quality and standards for platelet-rich plasma include a lack of standardized protocols, variations in preparation techniques, and regulatory limitations.
   Unlike pharmaceuticals, no universally accepted standard defines the optimal concentration of cells and growth factors. Different conditions may benefit from different formulations (leukocyte-rich versus leukocyte-poor).
   Quality assurance practices include process validation, testing and monitoring, traceability, and device selection.

   Evidence Level: Low; Consensus-Based Clinical Recommendation: Moderate

7. Bone Marrow Aspirate Concentrate (BMAC): Quality and Standards
   Answer: BMAC devices are expected to produce viable cells with cell viability rates of approximately 90%. The quality of BMAC is heavily dependent on the aspiration technique. Volume and site are important.
   There are no established standardized protocols. Consequently, there are variations in preparation technique limited by regulatory standards. Minimum requirements for BMAC include qualifying mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs).
   Different processing devices and methods produce different results.
   Quality assurance practices include process validation, testing and monitoring, traceability, and device selection

   Evidence Level: Low; Strength of Recommendation: Moderate

8. Minimum required quality control measures:
   Answer: The minimum required quality control measures for clinical purposes include final volume, platelet count, white blood cell (WBC) count, red blood cell (RBC) count, and the concentration factor relative to whole blood. Further, different processing devices and methods produce different results regarding final cell counts, viability, and volume.

   Evidence Level: Moderate; Consensus-Based Clinical Recommendation: Moderate

9. Minimum required platelets per injection:
   Answer: Studies show that a minimum of 4 billion and 10 billion as optimum count of platelets per injection is needed for a significant clinical effect in knee intraarticular injections. Even though limited, literature is available regarding spinal injections, based on other joints, a cumulative dose of around 10 billion platelets into structures of a FSU are recommended. There is literature showing intradiscal injections of PRP with greater than 10 times baseline platelet concentrations resulted in greater improvements in pain scores and functional outcomes at long-term follow-up compared to lower concentration PRP less than five times.

   Evidence Level: Low; Consensus-Based Clinical Recommendation: Moderate

10. It is essential to understand PRP and BMAC with multiple variations and the effectiveness, technical considerations, and complications with the spinal injections.

    Evidence Level: High; Consensus-Based Clinical Recommendation: High

11. Based on the available evidence and all available guidance, patient education is a crucial aspect of the success of regenerative medicine injections.

    Evidence Level: High; Consensus-Based Clinical Recommendation: High

12. What is the evidence of effectiveness for PRP and consensus-based clinical recommendations for intradiscal therapy.

    Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate

13. The evidence of effectiveness for BMAC and consensus-based clinical recommendations for intradiscal therapy.

    Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate.

14. The evidence of effectiveness and consensus-based clinical recommendations for epidural injections with PRP in managing low back and lower extremity pain due to degenerative disc pathology and other conditions.

    Evidence Level: III, Fair; Consensus-Based Clinical Recommendation: Moderate

15. The evidence of effectiveness and consensus-based clinical recommendations for facet joint intraarticular PRP and MSC injections in managing chronic low back pain.

    Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Moderate

16. The evidence of effectiveness and consensus-based

clinical recommendations for sacroiliac joint PRP injections.

Evidence Level: IV, Limited; Consensus-Based Clinical Recommendation: Low

17. The guidelines for administration of biologics include failure of conservative modalities, understanding of the risks and benefits, willingness to participate in rehabilitation program and appropriate consent with shared decision making.

    Evidence Level: High; Consensus-Based Clinical Recommendation: High

18. Risk stratification for regenerative medicine therapies, based on ASIPP guidelines: high risk for intradiscal therapy, moderate risk for epidural injections, low risk for facet joint injections, and low risk for sacroiliac joint injections.

    Evidence Level: Moderate; Consensus-Based Clinical Recommendation: Moderate

19. Antiplatelet and anticoagulant therapy guidelines in continuation, discontinuation, and re-establishment are utilized per ASIPP guidelines for low- and high-risk procedures.

    Evidence Level: Moderate; Consensus-Based Clinical Recommendation: Moderate

14.0 Conclusion

Both PRP and MSCs are used autologously to support and enhance the healing process. Their natural properties, including functional strengths and limitations, continue to be investigated. The guidelines presented have reviewed studies that both support and challenge the current clinical applications of these biologics. PRP is a concentration of inflammatory mediators and growth factors that complement tissue repair in injured areas. Biologics are increasingly viewed as a cost-effective and accelerated approach to healing and are becoming a reasonable alternative for patients who have not responded to standard-of-care treatments. Based on current literature, treatments targeting lumbar intervertebral discs, facets, and sacroiliac joints are typically performed only after a definitive diagnosis and following failure of conservative therapy. Published studies report outcomes of single-injection biologics for chronic pathology, demonstrating primarily short-term relief, with PRP being the most commonly used biologic in the lumbar spine.

Recent advancements, particularly in regenerative injection techniques, have shifted the focus toward a comprehensive treatment model addressing the entire FSU, offering a disease-modifying approach. The FSU, the smallest functional unit of the spine, consists of 2 vertebrae, an intervertebral disc, facet joints, and supporting ligaments. It plays a critical role in maintaining spinal stability, mobility, load distribution, and neural protection. The FSU absorbs shock, distributes mechanical loads, and protects the spinal cord and nerve roots. This publication aims to explore the concept of the FSU and evaluate the potential role of orthobiologics, such as PRP and MSCs, in managing back pain associated with various spinal conditions.

Emerging literature demonstrates the use of multiple-structure injections, which reflects an increasingly common clinical practice.

The continued clinical success of biologics will depend on standardizing their use, achieving consistent outcomes, and demonstrating overall reductions in healthcare costs. This can be accomplished through the publication of high-quality studies, which will enhance the predictability of biologic therapy. Advancing the science and application of regenerative medicine will require dedicated efforts from all stakeholders to further develop and optimize biologic therapies for the benefit of patients.

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Conflict of Interest

Dr. Soin has several patents in non-opioid pain pharmaceuticals and neuromodulation (SCS and PNS) and artificial intelligence, has stock options with Neuros Medical, has received equipment, materials, drugs, medical writing, gifts or other services from Avanos for research, and has other financial or nonfinancial interests with Alyea Therapeutics, Neuros Medical, Neuronoff, and Avanos.

Dr. Abd-Elsayed is a consultant for Medtronic, Curonix, Avanos, and Averitas.

Dr. Boddu is a Member of Scientific Advisory Board Apex Biologix and SAB TSOI, Bio Cuetics.

Dr. Khadavi is a paid consultant for medical education and product development for Arthrex, receives support for attending meetings, and is President and board member of TOBI.

Dr. Shah receives a "Train New Trainers Education Grant" State of California, made to institution, is a consultant for SPR Therapeutics & Vertex Pharma and is President, Orange County Medical Association.

Dr. Shounuck Patel receives payment or honoraria from Interventional Orthobiologics Foundation and Expert Education Institute and support for attending meetings.

Dr. Nabity is a share and stockholder with Greyledge BioTech, share and stockholder and CMO of Forever Labs, and receives payment or honoraria for IOF, Injection Trainer.

Dr. Calodney receives consulting fees from Medtronic, Nevro, Stryker, Saluda and PainTEQ.

Dr. Jordan has patents pending and issued for exosome delivery to brain.

Dr. Hirsch receives grants or contracts from the Neiman Health Policy Institute, is a Medtronic, Relievant, and Sanofi consultant, and is the Chair of CSMB of neurovascular studies for Balt: Rapid Medical.

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Appendix Table 1. *Sources of risk of bias and Cochrane Review collaboration.*

Bias Domain	**Source of Bias**		**Possible Answers**
Selection	(1) Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments.	Yes/No/Unsure
		Examples of inadequate methods are: alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.	
Selection	(2) Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or:	Yes/No/Unsure
		• for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"	
		• for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination	
		• for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome	
		• for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., cointerventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes"	
		• for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data	
Attrition	(6) Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/Unsure
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/Unsure
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/Unsure

Appendix Table 1 cont. ***Sources of risk of bias and Cochrane Review collaboration.***

Bias Domain	**Source of Bias**		**Possible Answers**
Performance	(10) Were cointerventions avoided or similar?	If there were no cointerventions or they were similar between the index and control groups.	Yes/No/Unsure
Performance	(11) Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered for several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all primary outcome measures.	Yes/No/Unsure
Other	(13) Are other sources of potential bias unlikely?	Other types of biases. For example: • When the outcome measures were not valid. There should be evidence from a previous or present scientific study that the primary outcome can be considered valid in the context of the present. • Industry-sponsored trials. The conflict of interest (COI) statement should explicitly state that the researchers have had full possession of the trial process from planning to reporting without funders with potential COI having any possibility to interfere in the process. If, for example, the statistical analyses have been done by a funder with a potential COI, usually "unsure" is scored.	Yes/No/Unsure

Adapted and Modified from: Furlan AD, et al; Editorial Board of the Cochrane Back, Neck Group. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673 (77).

Appendix Table 2. *Item checklist for assessment of randomized controlled trials of interventional pain management techniques utilizing IPM-QRB.*

		Scoring
I.	TRIAL DESIGN AND GUIDANCE REPORTING	
1.	CONSORT or SPIRIT	
	Trial designed and reported without any guidance	0
	Trial designed and reported utilizing minimum criteria other than CONSORT or SPIRIT criteria or trial was conducted prior to 2005	1
	Trial implies it was based on CONSORT or SPIRIT without clear description with moderately significant criteria for randomized trials or the trial was conducted before 2005	2
	Explicit use of CONSORT or SPIRIT with identification of criteria or trial conducted with high level reporting and criteria or conducted before 2005	3
II.	DESIGN FACTORS	
2.	Type and Design of Trial	
	Poorly designed control group (quasi selection, convenient sampling)	0
	Proper active-control or sham procedure with injection of active agent	2
	Proper placebo control (no active solutions into active structures)	3
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology/radiology/ortho, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 50 participants in the study without appropriate sample size determination	0
	Sample size calculation with less than 25 patients in each group	1
	Appropriate sample size calculation with at least 25 patients in each group	2
	Appropriate sample size calculation with 50 patients in each group	3
6.	Statistical Methodology	
	None or inappropriate	0
	Appropriate	1
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
7a.	For epidural procedures:	
	Poorly identified mixed population	0
	Clearly identified mixed population	1
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	2
7b.	For facet or sacroiliac joint interventions:	
	No diagnostic blocks	0
	Selection with single diagnostic blocks	1
	Selection with placebo or dual diagnostic blocks	2
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1

Appendix Table 2 cont. *Item checklist for assessment of randomized controlled trials of interventional pain management techniques utilizing IPM-QRB.*

		Scoring
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural, facet joint or sacroiliac joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for intradiscal injections, epidural, facet joint or sacroiliac joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 12 months for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., and 2 years or longer for intradiscal procedures and implantables	2
	18 months or longer for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., or 5 years or longer for intradiscal procedures and implantables	3
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	3
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Analysis of all Randomized Participants in the Groups	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13.	Description of Drop Out Rate	
	No description of dropouts, despite reporting of incomplete data or ≥ 20% withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1
	Groups similar with appropriate randomization and allocation	2
15.	Role of Co-Interventions	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	RANDOMIZATION	
16.	Method of Randomization	
	Quasi randomized or poorly randomized or not described	0

Appendix Table 2 cont. *Item checklist for assessment of randomized controlled trials of interventional pain management techniques utilizing IPM-QRB.*

		Scoring
	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High quality randomization (Computer generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call, pre-ordered list of treatment assignments, etc.)	2
VI.	ALLOCATION CONCEALMENT	
17.	Concealed Treatment Allocation	
	Poor concealment of allocation (open enrollment) or inadequate description of concealment	0
	Concealment of allocation with borderline or good description of the process with probability of failure of concealment	1
	High quality concealment with strict controls (independent assignment without influence on the assignment sequence)	2
VII.	BLINDING	
18.	Patient Blinding	
	Patients not blinded	0
	Patients blinded adequately	1
19.	Care Provider Blinding	
	Care provider not blinded	0
	Care provider blinded adequately	1
20.	Outcome Assessor Blinding	
	Outcome assessor not blinded or was able to identify the groups	0
	Performed by a blinded independent assessor with inability to identify the assignment-based provider intervention (i.e., subcutaneous injection, intramuscular distant injection, difference in preparation or equipment use, numbness and weakness, etc.)	1
VIII.	CONFLICTS OF INTEREST	
21.	Funding and Sponsorship	
	Trial included industry employees	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only with supporting entity unrelated to industry	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
22.	Conflicts of Interest	
	None disclosed with potential implied conflict	0
	Marginally disclosed with potential conflict	1
	Well disclosed with minor conflicts	2
	Well disclosed with no conflicts	3
	Hidden conflicts with poor disclosure	–1
	Misleading disclosure with conflicts	–2
	Major impact related to conflicts	–3
TOTAL		48

Source: Manchikanti L, et al. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290 (78).

Appendix Table 3. *Bias domains included in the ROBINS-E tool, with a summary of the issues addressed for cohort studies.*

Bias domain	**Issues Addressed**	**Possible Answers**
Bias due to confounding	Whether: • all important confounding factors were controlled for using appropriate methods; • the confounding factors were measured validly and reliably by the variables available; and • variables after the start of the exposure window (and that could have been affected by the exposure) were inappropriately controlled for.	Yes/No/Unsure
Bias arising from measurement of the exposure	Whether: • the measure of exposure used in the study well characterizes the exposure metric of interest; • there was likely to be error in, or misclassification of, the exposure measurements in the study; • there was differential measurement (or misclassification) error; and • non-differential measurement (or misclassification) error would have biased the effect estimate.	Yes/No/Unsure
Bias in selection of participants into the study	Whether: • start of follow-up and start of the exposure window were the same; • selection of participants into the study (or into the analysis) was based on participant characteristics observed after the start of the exposure window; • (if applicable) these characteristics were influenced by exposure (or a cause of exposure) and influenced by outcome (or a cause of the outcome); and • (if applicable) adjustment techniques were used to correct for the presence of selection biases.	Yes/No/Unsure
Bias due to post-exposure interventions	Whether: • there were post-exposure interventions influenced by prior exposure; and • (if applicable) the analysis corrected for the effect of these post-exposure interventions.	Yes/No/Unsure
Bias due to missing data	Whether: • complete data on exposure status, the outcome, and confounders were available for all or nearly all participants; • (for complete case analyses) omission from the analysis is likely to be related to the true value of the outcome and predictors of missingness were included in the analysis model; and • (for analyses with imputed data) imputation was performed appropriately.	Yes/No/Unsure
Bias in measurement of the outcome	Whether: • measurement or ascertainment of the outcome is likely to have differed between exposure groups or levels of exposure; • outcome assessors were aware of study participants' exposure history; and • (if applicable) assessment of the outcome were likely to have been influenced by knowledge of participants' exposure history.	Yes/No/Unsure
Bias in selection of the reported result	Whether: • the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple exposure measurements within the outcome domain; • the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple outcome measurements within the outcome domain; • the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple analyses of the data; and • the numerical result being assessed is likely to have been selected, on the basis of the results, from multiple subgroups of a larger cohort.	Yes/No/Unsure

Source: Higgins JPT, Morgan RL, Rooney AA, et al. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). *Environ Int*. 2024 Apr;186:108602 (79).

Appendix Table 4. *Item checklist for assessment of nonrandomized or observational studies of interventional pain management techniques utilizing IPM-QRBNR.*

		Scoring
I.	STUDY DESIGN AND GUIDANCE REPORTING	
1.	STROBE or TREND Guidance	
	Case Report/Case Series	0
	Study designed without any guidance	1
	Study designed with minimal criteria and reporting with or without guidance	2
	Study designed with moderately significant criteria or implies it was based on STROBE or TREND without clear description or the study was conducted before 2011 or similar criteria utilized with study conducted before 2011	3
	Designed with high level criteria or explicitly uses STROBE or TREND with identification of criteria or conducted prior to 2011	4
II.	DESIGN FACTORS	
2.	Study Design and Type	
	Case report or series (uncontrolled – longitudinal)	0
	Retrospective cohort or cross-sectional study	1
	Prospective cohort case-control study	2
	Prospective case control study	3
	Prospective, controlled, nonrandomized	4
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 100 participants without appropriate sample size determination	0
	At least 100 participants in the study without appropriate sample size determination	1
	Sample size calculation with less than 50 patients in each group	2
	Appropriate sample size calculation with at least 50 patients in each group	3
	Appropriate sample size calculation with 100 patients in each group	4
6.	Statistical Methodology	
	None	0
	Some statistics	1
	Appropriate	2
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
7a.	For epidural procedures:	
	Poorly identified mixed population	1
	Poorly identified mixed population with large sample (≥ 200)	2
	Clearly identified mixed population	3
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	4
7b.	For facet or sacroiliac joint interventions:	

Appendix Table 4 cont. *Item checklist for assessment of nonrandomized or observational studies of interventional pain management techniques utilizing IPM-QRBNR.*

		Scoring
	No specific selection criteria	1
	No diagnostic blocks based on clinical symptomatology	2
	Selection with single diagnostic blocks	3
	Selection with placebo or dual diagnostic blocks	4
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural, facet joint or sacroiliac joint procedures, etc. and 6 months for intradiscal procedures and implantables	1
	3 to 6 months for intradiscal injections, epidural, facet joint or sacroiliac joint procedures, etc., or 1 year for intradiscal procedures or implantables	2
	6 months to 12 months for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., and 2 years or longer for intradiscal procedures and implantables	3
	18 months or longer for intradiscal injections, epidurals, facet joint or sacroiliac joint procedures, etc., or 5 years or longer for intradiscal procedures and implantables	4
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	3
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Description of Drop Out Rate	
	No description despite reporting of incomplete data or more than 30% withdrawal	0
	Less than 30% withdrawal in one year in any group	1
	Less than 40% withdrawal at 2 years in any group	2
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	No groups or groups dissimilar with significant influence on outcomes	0
	Groups dissimilar without significant influence on outcomes	1
	Groups similar	2
14.	Role of Co-Interventions	
	Dissimilar co-interventions or similar co-interventions in some of the participants	1

Appendix Table 4 cont. ***Item checklist for assessment of nonrandomized or observational studies of interventional pain management techniques utilizing IPM-QRBNR.***

		Scoring
	No co-interventions or similar co-interventions in majority of the participants	2
V.	ASSIGNMENT	
15.	Method of Assignment of Participants	
	Case report/case series or selective assignment based on outcomes or retrospective evaluation based on clinical criteria	1
	Prospective study with inclusion without specific criteria	2
	Retrospective method with inclusion of all participants or random selection of retrospective data	3
	Prospective, well-defined assignment of methodology and inclusion criteria (quasi randomization, matching, stratification, etc.)	4
VI.	CONFLICTS OF INTEREST	
16.	Funding and Sponsorship	
	Trial included industry employees with or without proper disclosure	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement or no information available	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
TOTAL MAXIMUM		48

Source: Manchikanti L, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of non-randomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317 (80).