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ALTERNATIVE TREATMENTS FOR PAIN MEDICINE (M JONES, SECTION EDITOR)

Biologic Therapy in Chronic Pain Management: a Review of the Clinical Data and Future Investigations

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Abstract

Purpose With the aging population, it is clear that the demand for future chronic pain treatment modalities is at an all-time high. One of the newest treatment modalities that is gaining popularity with both practitioners and patients alike is that of regenerative medicine and the use of stem cells to treat chronic painful conditions. This article aims to distill the most recent, available data from both laboratory research and clinical trials to better illuminate the potentials for these therapies in the treatment of chronic pain.

Recent Findings There are numerous investigations underway using mesenchymal stem cells (MSCs) to treat painful, largely degenerative conditions. A large majority of these investigations focus on osteoarthritis of the knee and have demonstrated significantly improved pain scores. Some of these investigations have demonstrated significantly increased articular cartilage and meniscus growth as well as improved function. These studies have been smaller (*n*, 18) and need to be corroborated on a macrolevel. Platelet-rich plasma (PRP)-based therapies have been most extensively studied in the treatment of knee osteoarthritis. Multiple prospective and randomized trials and meta-analyses have afforded level I evidence in support of PRP's safety and efficacy in chronic knee pain demonstrating both decreased pain (via VAS) and increased functional status (via WOMAC and IKDC). There have been randomized controlled trials examining PRP therapies in treatment degenerative disc disease (intradiscal treatment), facet arthropathy (intra-facet injections), and sacroiliitis (SIJ) which have all yielded similar positive results. Each RTC demonstrated decreased pain scores and increased function but lacks the scale to derive concrete guidelines. Newer investigations are underway examining modified PRP formulas with increased fibrin (PRF) or various growth factors (PRGF) and have shown positive outcomes with respect to osteoarthritic conditions in small trials. Animal trials are underway further investigating these therapies as well as specific gene modulation therapies.

Summary This review of the most recent investigations into the application and uses of biologic stem cell–derived treatments for chronic painful conditions should act to illustrate the growing, favorable data for these types of modalities both with respect to pain control and functional improvement.

Keywords Stem cells · Biologic therapy · Chronic pain · Platelet-enriched plasma · Platelet-rich fibrin · PRP · PRF · PRGF · Mesenchymal stem cells · MSC · Gene therapy · Regenerative medicine

Introduction

For the first time in history, it was predicted that by the year 2034, the gross number of people ages 65 and older will outnumber those under the age of 18 [1]. Understanding that one of the most common causes of chronic pain, arthritis, is a largely age-related degenerative condition, it is clear that the demand for future chronic pain treatment modalities is at a record high. A MEPs (US Medical Expenditure Panel survey) examined the total cost expenditure of just arthritic-related conditions, and based on 2013 data, they found that already $135.9 to $157.5 billion dollars was spent on arthritic-related

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medical conditions [2]. To further emphasize the socioeconomic burden of these chronic painful conditions, this survey calculated the projected lost earnings potential of that population to be another $163.7 billion dollars [1, 2]. Given the growing importance of the issue and the deterrence from chronic opioid use, the field of chronic pain is under the microscope both politically and clinically in order to develop much needed advances [3].

One such research avenue that has become widely popularized is that of stem cell therapies and regenerative medicine. While the concept of stem cell treatments is certainly not new, the harvesting methods now making autologous donation a readily available option have aided to decrease both the ethical and immunologic risks associated with the treatment [4]. Specific modalities such a mesenchymal stem cells and platelet-enriched plasma have now become important adjuncts in the non-surgical treatment algorithm for chronic pain. These therapies are believed to be multipotent stem cells that have the unique potential to regenerate lost cartilage, connective tissue, or even bone, thereby not only decreasing the painful symptoms but also restoring function to their targeted sites. The regenerative aspect of this treatment has practitioners and patients alike very excited. There have been clinical investigations into the use of stem cells for anything ranging from intrathecally to improve motor function in those with severe spinal cord injuries to intradermally for cosmetic purposes such as for acne scarring or alopecia [4, 5].

This article aims to distill the most recent, available data from both laboratory research and clinical trials to better illuminate the potentials for these therapies in the treatment of chronic pain. This review will define each therapy on a molecular level, discuss the tangible harvesting processes, and examine the data regarding the potential benefits for each of these modalities both with regard to pain control and regenerative potential. A summary of the current pain modalities discussed in this review and those under investigation can be found in Table 1.

MSCs: Overview

Mesenchymal stem cells (MSCs) are adult multipotent stem cells that possess unique characteristics like the ability to differentiate into a specific subset of cell phenotypes and to modulate important immune and inflammatory functions [6, 7]. Given these particular properties, MSCs have become one of the most widely researched therapeutic drug targets for degenerative joint diseases like osteoarthritis (OA) and diseases related to chronic pain. Originally isolated from whole bone marrow cultures in the 1970s, the International Society for Cell Therapy has since established specific guidelines to properly identify and distinguish MSCs for therapeutic use. Currently, there are three criteria used to identify MSCs. Specifically, MSCs are plastic-adherent cells that express CD105, CD73, CD90, and HLA-DR surface molecules. They lack the expression of CD45, CD34, CD14 or CD11b, and CD79a or CD19 and are capable of differentiation in vitro [6].

MSCs are typically sourced from bone marrow; however, they can be harvested from other autologous and allogenic sources including adipose tissue, peripheral blood, placental tissues, umbilical cords, tendons, and periodontal tissue [6–8]. Despite bone marrow being the most common source, adipose tissue has recently gained popularity for its abundant nature and accessibility [8]. Adipose-derived MSCs are acquired via liposuction with the sub-patellar fat-pad region being one of the most common areas to source from. In order to formulate a more concentrated product, adipose tissue is mixed with collagenase 1 to break down the liposomes, and these contents are then separated through a process of centrifugation [6].

Given MSCs' ability to differentiate into chondrocytes as well as modulate important immune functions, extensive research has been dedicated to further understand precisely how these cells can be of benefit for chronic diseases like OA. In OA, the damaged articular cartilage is limited in its capacity to repair itself due to its avascular nature [6]. Despite this lack of blood flow, it has been reported that MSCs in vivo migrate to areas of cartilage ischemia and damage [6]. Once they have entered the joint space and are under appropriate environmental conditions, MSCs can differentiate into distinct cells of the mesenchymal germ cell layer including osteoblasts, adipocytes, and chondrocytes, which is most important as it pertains to OA [6, 7]. However, studies have still not identified whether articular cartilage replenishment and repair are directly due to chondrocyte differentiation or paracrine mechanisms in the form of exosomes.

Exosomes provide the means for intercellular communication and transfer substances like lipids, nucleic acids, and proteins between cells to elicit biological responses [6]. MSC exosomes are abundant in microRNA, and studies suggest that this abundance contributes to OA suppression and promotes cartilage regeneration [6]. In a study to further understand the role of how exosomes participate in cartilage repair, Tao et al. reported that human MSC exosomes overexpressed with microRNA-140-5p had a positive effect on the regeneration of cartilage and protective benefit through the suppression of OA in rat models [9]. Furthermore, several microRNA sequences have been linked to the expression and upregulation of SOX9 and aggrecan resulting in cartilage homeostasis, cartilage maintenance, and the restoration of the extracellular matrix [6].

In addition to cell differentiation and cartilage maintenance, MSCs play an integral role in local immune regulation. In response to synovial membrane injury and inflammation, MSCs secrete various chemokines including SDF-1a, MCP-1, and MCP-2 [6]. These chemokines attract various immune regulatory cells including monocytes, macrophages,

Table 1 Current therapeutic pain modalities and those under investigation

Characteristic features	Mesenchymal stem cells	Platelet-rich plasma	Platelet-rich fibrin	Plasma rich in growth factors	Autologous conditioned serum
Source	Autologous and allogenic sources including bone marrow, adipose tissue, peripheral blood, placental tissues, umbilical cords, tendons, periodontal tissue, and others [6, 7, 9]	Autologous venous blood [18]	Autologous venous blood [29]	Autologous venous blood [31]	Autologous venous blood [3]
Composition	Undifferentiated stem cells that express CD105, CD73, CD90, and HLA-DR surface molecules and lack the expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 [6]	Growth factors and cytokines released from activated platelets [16]	PRP within a dense fibrin matrix that consists of growth factors and cytokines when platelets and fibrin are activated [29]	Resembles PRP but platelets are activated for maximal release of growth factors [31]	Autologous blood enriched with interleukin-1 receptor antagonist (IL-1Ra) [3]
Mechanism of action	Differentiates into multiple cell types native to the specific site Immunosuppressive and anti-inflammatory potential through chemokine secretion Regeneration of bone and tissues through MSC exosomes overexpressed with specific microRNA sequences [6, 7, 9]	Anti-inflammatory and regenerative potential through platelet growth factor and chemokine secretion [16, 20]	Anti-inflammatory and regenerative potential through platelet and fibrin activation causing immediate release of growth factors and cytokines embedded in a fibrin clot that can be applied to tissue or injected [29]	Anti-inflammatory and regenerative potential through the release of various growth factors Affects stem cell activity and gene regulation [32]	Suppresses inflammation through anti-inflammatory cytokines including IL-4, IL-10, IL-13, and IL-1Ra[3]
Application	Osteoarthritis-related joint pain with therapeutic potential for chronic back pain related to degenerative changes [11, 13]	Osteoarthritis-related joint pain with therapeutic potential for chronic back pain related to degenerative changes [17, 20, 22]	Dental surgeries Therapeutic potential for chronic pain management currently under investigation [30]	Chronic back pain related to degenerative changes [34]	Radiculopathy-related pain [3, 35, 36]

lymphocytes, and dendritic cells to the damaged site and subsequently coordinate repair mechanisms of damaged bone and cartilage [6, 7]. Activated MSCs also secrete PGE2, IDO2, and NO resulting in direct and indirect immune cell suppression [6]. Studies suggest that the biological responses that occur can effectively suppress T cell proliferation and dendritic cell maturation, can induce T cell apoptosis ultimately increasing the number of regulatory T cells, and mitigate rejection and disease transmission through an effect on B cells [6, 7]. It is important to note that this immunomodulatory function varies among individuals, tissue sources, culture conditions, and activation states suggesting a need to standardize this process [6, 7].

Applications and Data

In regard to clinical outcomes, multiple animal models and clinical trials pertaining to OA intervention with MSCs, particularly in the knee, consistently demonstrate positive outcomes. After inducing OA in rabbits through the resection of the anterior cruciate ligament, Toghrarie et al. reported significant improvement and repair of cartilage tissue at 20 weeks after the rabbits' knees were injected with 1×10 [6]/mL of adipose MSCs. Changes in the cartilage tissue were evaluated on the basis of imaging, morphology, and histology [10]. While clinical trials are underway worldwide, preliminary data remain promising and describe similar results. In one particular case report, Centeno et al. reported that severe OA of the knee significantly improved after the injection of bone marrow MSCs. In order to enhance cartilage growth, the MSC suspension was mixed with 10% lysate and 10 ng dexamethasone prior to injection. Six months after the intervention, MRI imaging was significant for increased articular cartilage and meniscus growth [11]. Additionally, there were significant improvements in both function, based on joint range of motion testing and pain based on visual analog scale scores [11].

This small case report first demonstrating in human subjects the potential for cartilage regeneration has been reproduced by other clinical studies as well. Jo et al. examined the use of intra-articular MSCs and demonstrated similar data to the Centeno report. This was another smaller study, enrolling 18 subjects with osteoarthritis of the knee categorized as grade II or higher on the Kellgren-Lawrence scale, treated each with various concentrations of MSCs. They found that a higher injection dose of adipose-derived MSCs of 1.0×10^8 significantly improved knee joint function and cartilage growth and decreased pain VAS scores 6 months after injection ($P < 0.001$) when compared to both the medium dose group (5.0×10 [7]) and low dose group (1.0×10 [7]) which only showed mild and no improvement, respectively [12].

In addition to degenerative joint changes of the knee, there are multiple studies focused on understanding the therapeutic potential of MSCs as it pertains to chronic back pain. Orozco et al. performed a pilot study in 2009 evaluating the safety and efficacy of autologous MSCs in the management of chronic back pain in patients diagnosed with lumbar disc degeneration. Ten patients were enrolled in the study and were treated with autologous expanded bone marrow–derived MSCs that were injected into the area of the nucleus pulposus of affected joints. Compared with basal levels of pain and disability, improvement was statistically significant at 3, 6, and 12 months with 85% of the total improvement occurring during the first 3 months [13]. Furthermore, although there was no difference in disc segment heights based on MRI evaluation, water content of affected disc segments showed statistically significant improvement ($P < 0.05$) in the water ratio at 12 months when compared to healthy segments [13]. Additionally, Sanapati et al. conducted a systematic review and determined that not only are MSCs in spinal cord injuries and intervertebral disc repair both safe and effective treatments but also all types of MSCs including bone marrow, adipose, and synovial tissue sources resulted in significant inhibition of disc degeneration when compared to non-MSC treatments. Furthermore, several in vitro and in vivo studies have demonstrated that when MSCs are combined with growth factors such as those found in PRP for intradiscal injection, intervertebral disc cell proliferation and chondrogenic matrix metabolism are significantly enhanced [3]. This suggests that the combination of MSCs and growth factors enhances the potential for cartilage repair and the therapeutic potential for managing degenerative joint diseases like facetogenic and discogenic back pain.

PRP: Introduction

Platelet-rich plasma (PRP) is defined as autologous plasma with greater than baseline concentration of platelets. It has been used in a variety of fields, including oral and maxillofacial surgery, dermatology, and cosmetic surgery to augment wound healing, and in orthopedics and sports medicine to improve symptoms of tendonapathy, ligamentous injuries, and joint disorders [14, 15]. In chronic pain management, injections of PRP alone and in combination with MSCs have proven efficacious in improving pain and functionality in patients with knee and back pain. The beneficial effects of PRP are thought to derive from the growth factors and immunomodulatory cytokines released from the platelets and delivered to target tissues in supraphysiologic concentrations. These proteins—which include but are not limited to transforming growth factor beta, platelet-derived growth factor, insulin-like growth factor 1, epidermal growth factor, and stromal-derived factor 1 alpha—augment the body's natural healing cascade by promoting protein transcription, cell

proliferation and migration, collagen synthesis, and angiogenesis and by modulating inflammation [16].

Preparation

Currently, there are multiple methods and protocols for PRP preparation, which can be performed in a laboratory or at the point of care using commercially available kits (i.e., GPS System III by Zimmer Biomet) [17]. A majority of these protocols employ a centrifuge or density gradient cell separator to separate whole blood into its components. An initial "hard" spin separates the red blood cells, buffy coat (platelets and white blood cells), and plasma. The buffy coat and plasma layers undergo a second "soft" spin which finely separates these components, producing a platelet-concentrated fraction (PRP), which is then injected into damaged tissues [18]. Beyond this basic framework, much variability exists in preparation methods and the composition of PRP they produce. In order to standardize PRP reporting, Mautner and colleagues propose a PRLA classification system that characterizes PRP according to its platelet concentration, volume of PRP delivered, presence or absence of leukocytes, presence or absence of red blood cells, and whether platelets are activated before being delivered to target tissue [19].

Application of Data

Within the field of chronic pain management of joint disorders, PRP-based therapies have been most extensively studied in the treatment of knee osteoarthritis. Multiple prospective and randomized trials have given rise to several recent systematic reviews and meta-analyses, affording ample level I evidence in support of PRP's safety and efficacy in chronic knee pain [17, 20–22]. In the largest meta-analysis (as of 2020), Trams and colleagues analyzed 38 studies including 2962 patients that evaluated PRP injections for knee arthritis. Pooled estimates showed significant differences in reported pain (via VAS) in favor of PRP over HA and placebo, though differences were non-significant between PRP and steroid. In the domains of functional status via WOMAC and IKDC scores, pooled estimates also showed significant differences in favor of PRP [17].

Application of PRP to the management of chronic back pain is less studied than for knee osteoarthritis. Based on available evidence, PRP shows promise as an effective therapy for intradiscal, facetogenic, and sacroiliac joint-related pain. However, more well-designed RCTs are needed in these areas before definitive conclusions can be made.

To date, one RCT studying intradiscal PRP injections has been published. In 2016, Tuakli-Wosornu and colleagues demonstrated that patients who received intradiscal PRP had improved pain, function, and satisfaction at 8 weeks compared to those who received an Omnipaque contrast and that functional improvements persisted to 1-year post-intervention [23]. A systemic review of available studies on intradiscal PRP concluded that PRP results in statistically significant reductions in pain, but determinations of clinical significance and efficacy could not be made owing to the lack of high-quality evidence on the subject [24].

The only published RCT studying PRP injection into the sacroiliac joint randomized patients to receive either PRP or steroid injections found that at 3 months post-intervention, both groups showed significant reduction in pain from baseline, though 90% of the PRP group reported satisfactory pain relief vs 25% of the steroid group [25]. A systematic review of available studies found insufficient high-quality evidence to draw conclusions on the effectiveness of PRP for SIJ-related pain [26].

In the only published prospective RCT studying PRP for lumbar facet syndrome, Wu and colleagues (2016) found that patients who received a PRP injection and those who received a corticosteroid/local anesthetic injection had significant improvements in pain and functional status immediately and at 1 month, but at 3 months, pain relief and functional status were greater in the PRP group [27]. A recent review notes the paucity of high-quality evidence to validate the results of this trial [28].

Platelet-Rich Fibrin

Platelet-rich fibrin (PRF) is considered a second-generation PRP consisting of PRP within a dense fibrin matrix. In the process of its preparation from whole blood, platelets and fibrin are activated, causing immediate release of growth factors and cytokines and a fibrin clot. The platelets and the release molecules are concentrated and embedded in the clot, which takes the form of a gelatinous biomembrane that can then be either applied to tissue or injected. Purported advantages over PRP include simpler preparation, lower cost, more continuous and stable release of growth factors and cytokines, and a stable architecture that allows it to be applied as a biomaterial [29]. PRF use is best documented and research in the use of dental surgery. Interventional pain physicians are beginning to adopt its practice. For example, a non-randomized controlled trial comparing sacroiliac PRF and PRP injections found statistically significant differences in favor of PRF in pain improvement measured by VAS [30]. More studies are needed to validate the efficacy of PRF in chronic pain management.

Plasma Rich in Growth Factors: MOA and Data

Plasma rich in growth factors (PRGF) is harvested from autologous patient blood via centrifugation, with extraction of

concentrated platelets, similar to platelet-rich plasma (PRP), but then activated for maximal growth factor release. PRGF is advantageous over PRP by only requiring one centrifugation step and remains leukocyte free, avoiding high levels of pro-inflammatory cytokines [31]. PRGF allows delivery of proteins and growth factors such as transforming growth factor B (TGF-B), insulin-like growth factor (IGF), and vascular endothelial growth factor (VEGF) to the site of injury that promote regeneration healing of tissue and bone. These factors are crucial for initiation of bone callus formation, matrix proliferation, chondrocyte maturation, and callus hardening.

Furthermore, PRGFs have been shown to effect stem cell activity from a variety or origins. PRGFs have been shown to upregulate gene expression of type I collagen a1 and bone morphogenic proteins (BMPs) via real-time PCR by Okado et al. (2016) in human dendritic stem cells [32]. Tang and colleagues (2015) experimented on PRGF for chondrogenic induction of adipose stem cells, showing significantly increased collagen II accompanied by aggrecan expression in a rabbit model [33].

Kirchner and Anitua (2016) preformed a retrospective observational pilot study on 86 individuals with lumbar disc degeneration at 6 months after infiltrating PRGF under fluoroscopic guidance into the intervertebral discs and facet joints. Kirchner and Anitua showed reduction of visual analog score (VAS) over time at 1 month, 3 months, and 6 months, touting 90.7% of patients with excellent scores after study completion at 6 months and an additional 8.1% reporting moderative improvement ($P < 0.0001$), without any major adverse events [34]. While this amounts to extremely high positive results, drawbacks to this study include multiple injections and observational unreliability. Sanapati et al. (2018) grouped this observational study with other observational studies of moderate quality, revealing that qualitative evidence is level III (on scale of level I to level V) using a qualitative modified approach to grading of evidence based upon best-evidence synthesis for PRGF [3].

Autologous Conditioned Serum (Orthokine and Regenokine): MOA and Data

Autologous conditioned serum (ACS) is an autologous blood product enriched in interleukin-1 receptor antagonist (IL-1Ra), a naturally occurring inhibitor of IL-1. ACS was marketed as Orthokine in Germany and Regenokine in USA, working as an anti-inflammatory treatment to suppress joint or back pain. Dr. Peter Wehling, an Orthokine pioneer, postulated that inflammation was equally a cause of tissue damage as well as a symptom of mechanical joint problems. ACS differs from platelet-rich plasma by focusing on suppression of inflammation rather than simply rebuilding the joint.

ACS has been described as a source of anti-inflammatory cytokines including IL-4, IL-10, IL-13, and IL-1Ra[3]. IL-1 has been deemed a "biochemical sensitizer" of nerve roots in radiculopathy, making ACS's high concentrations of IL-1Ra promising as a new treatment option for patients with radicular pain [3]. ACS-Orthokine has been studied in one randomized controlled trial. Eighty-four patients with chronic lumbar radicular pain were divided into three groups to contrast ACS versus local + triamcinolone versus triamcinolone alone. Results showed improvement in all three groups with significance over 26 weeks; however, ACS-Orthokine showed a consistent pattern of superiority over both triamcinolone groups with VAS pain relief [35]. This RCT has drawbacks of multiple injections, as well as no resultant difference in functional improvements across groups [3].

ACS was tested under prospective evaluation in a small study by Kumar et al. in 2015. Twenty patients with unilateral lumbar radiculopathy received interlaminar injections under fluoroscopy with ACS, followed for 6 months [36]. Results showed positive improvement in pain relief and functionality (VAS improving 6.95 to 2.0), arguing ACS can modify radiculopathy disease course [3].

Specific Target Genes as Potential for Future Treatments and Modulation

Proenkephalin

Enkephalins are endogenous opioid peptides derived from a proenkephalin precursor protein, vital in regulating many physiologic functions including pain perception. Sun and colleagues studied the nociceptive effects of intrathecal administration of human bone marrow mesenchymal stem cells genetically modified with human proenkephalin genes in a rat model of sciatic chronic constrictive injury [37]. By evaluating ipsilateral paw withdrawal times to thermal hyperalgesia, Sun et al. (2017) demonstrated significant withdrawal threshold and latency as effective pain relief. This study shows genetically modified bone marrow stem cells could be a valid alternative treatment for neuropathic pain with vast potential for future development [37].

SUMO

Dynamic modification involving small ubiquitin-like modifier (SUMO) has emerged as a new mechanism of protein regulation as modulation in the NFkB pathway with anti-inflammatory effects. SUMO is also shown to augment PPAR in anti-inflammatory activity. SUMO regulation controls biological outcomes of growth factors FGF2, TGF-b, and IGF-1 on cartilage through transcription of Smad and Elk-1. Because many inflammatory signaling pathways converge on

NFkB and MAPK activation and with MAPK pathways having a common Elk-1 target, Elk-1 may play a central role in chondrocyte homeostasis [38]. Smad is pivotal to TGF-B/BMP-mediated anabolic chondrocyte activity, regulating transcription via SUMOylation, which may be worth further investigation [39].

Further models have postulated that inhibiting the SUMOylation of CRMP2 highlights a central role in pain transmission signaling via voltage-gated ion channels. NaV1.7 ion channels have been linked to human pain syndromes with upregulated expression. A selective reduction in NaV1.7 ion channel surface expression and current density was observed in rodent and human sensory neurons expressing mutant CRMP2 that lacked SUMO phosphorylation site [40]. Defecting NaV1.7 channels is challenging and must be selective or partial, as complete obliteration of NaV1.7 channels may render a patient unable to feel even normal levels of discomfort, which could lead to more harm than good.

miR-9-5p

After peripheral nerve injury, effective axon regeneration is achieved mainly by precise regulation of gene expression. MicroRNAs have an important epigenetic function in regulating gene expression and therefore may serve an important role in impairing axon regeneration. MicroRNA-9 (miR-9) at high endogenous levels was shown to inhibit axon regeneration in vitro and in vivo mouse models [41]. This is mediated by directly suppressing FoxP1, which Jiang et al. showed as necessary for efficient peripheral axon regeneration. Furthermore, miRNA-9 enhancement has been shown to affect the regulation of osteoblast differentiation from mesenchymal stem cells and induce defective trafficking of voltage-gated sodium ion channels in mouse models [42, 43]. These may play alternative pathways in effecting chronic pain physiology and worthy of further investigation. While the role of miRNA modification in post-mitotic axonal growth remains much unknown, microRNAs are emerging as a novel cellular mechanism of gene regulation in stem cells.

Conclusion

This review of the most recent investigations into the application and uses of stem cell treatment for chronic painful conditions should act to illustrate the growing, favorable data for these types of modalities, most notably PRP injections. With the lack of high-quality randomized controlled trials on the subject, the large majority of the evidence for chronic pain treatments is ranked as level II to level IV. And while this review does not describe any new panaceas in the field of pain management, one ought to be particularly impressed by the level I evidence for PRP intra-articular knee injections with respect to pain control [17, 20, 22]. This is a milestone event in the field of interventional pain and should act to solidify the notion that there is strong clinical data regarding these biological agents.

With the growing clinical data and future investigational data into more specific gene modulation therapies, it is not unrealistic to believe that these forms of treatments may one day replace the current steroid-based interventional modalities and act to provide longer relief and greater clinical benefit to this patient population. Moreover, in conjunction with many other medical fields that have worked to emphasize the importance of preventive medicine, pain management clinicians may one day utilize the regenerative potential of these therapies to better treat their patients and combat the growing socioeconomic costs of this condition [6, 7, 9, 22].

Declarations

Conflict of Interest Dr. Mark Motejunas, Dr. Devin Reed, Dr. Cleao Carter, Dr Ken Ehrhardt, and Dr. Lauren Bonneval have no conflict of interests to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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