From: Integrative Pain Management
Weil Integrative Medicine Library
Oxford University Press 2016

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Regenerative Injection Therapies for Pain: Traditional, Platelet Rich Plasma and Biocellular Prolotherapy

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Key Points

- Traditional medical models often do not offer clear-cut treatment options or outcomes for many types of musculoskeletal pain or sports injuries.
- Prolotherapy is a method of regenerative injection treatment that stimulates musculoskeletal repair and healing, reducing or eliminating pain, with low medical risk and high success rate.
- Types of prolotherapy include original dextrose, platelet rich plasma (PRP), and biocellular (stem cell) prolotherapy. The choice of which to use depends on the specific problem and severity.
- An integrative approach, looking at the history of injury and how it has affected the system as a whole, is important in order to offer the best options to the patient in pain.

Introduction

Musculoskeletal pain represents a major health problem throughout the world. No other class of disorders affects more people, leads to a higher incidence of disability, or places a higher financial burden on healthcare systems.[1] There are over one million knee surgeries performed every year, including meniscus surgery, however controversy exists about whether outcomes are any better than more conservative approaches.[2]

Shoulder injuries, including rotator cuff tendon problems, are also frequent,[3] however there is an unclear consensus about appropriate treatment or the value of surgery.[4] Low back pain, including disc herniations, is another common medical complaint, and is the second most frequently reported illness in industrialized countries, next to the common cold.[5] Yet again, there is uncertainty or controversy about the best treatment options or the usefulness of back surgery for this condition.[6] Sports injuries such as hamstring tendinopathies are common and can be disabling, but several traditional conservative treatments, including physiotherapy and nonsteroidal anti-inflammatory drugs, have yielded inconsistent results.[7]

Prolotherapy is a method of regenerative injection treatment designed to stimulate musculoskeletal healing[8] for these, as well as other musculoskeletal and joint pain, with a high success rate and low medical risk. Prolotherapy is short for "proliferation" therapy because it stimulates the repair and proliferation of new healthy tissue at sites of injury. Because prolotherapy is designed to repair tissue, it is a long-term solution rather than just a palliative measure. There are three distinct types of prolotherapy: Traditional dextrose prolotherapy, which originated in the 1930s and continues to be used successfully to this day; platelet rich plasma (PRP) prolotherapy, in use over the past ten years; and biocellular (stem cell) prolotherapy, which has gained popularity in the last five years. This chapter discusses the different types of prolotherapy, indications for use and case examples.

Prolotherapy: The Original Regenerative Medicine

Prolotherapy is a method of injection treatment designed to stimulate musculoskeletal connective tissue healing.[9] Prolotherapy was "discovered" in the 1930s, and works by raising local growth factor levels to promote tissue repair and regeneration.[10] Multiple studies confirm the effectiveness of prolotherapy in the resolution of musculoskeletal pain, such as low-back pain,[11,12] neck pain and whiplash injuries,[13] knee pain including patella tendonopathy,[14] meniscal tears[15] and knee osteoarthritis,[16,17] and shoulder pain (including rotator cuff injuries),[18] coccyxdynia,[19] ankle pain,[20] tennis and golfer's elbow,[21] plantar fasciits,[22] chronic tendonitis/ tendonosis[23] including achilles tendonitis/ tendonosis,[24] sports injuries such as high hamstring tendinopathy,[25] morton's neuroma pain,[26] and other joint pain or musculoskeletal pain and pain related to osteoarthritis.[27]

Earl Gedney, an osteopathic general surgeon, is reported to be the first physician to do this procedure in 1936, with his first patient being himself. After sustaining a traumatic injury to his hand, resulting in a sprained, painful, and

unstable thumb, he researched everything he knew about medicine, finally extrapolating from the then practice of "herniologists." These specialists in hernia repair would inject an irritating solution into the ligamentous fibrous hernia ring, stimulating connective tissue repair of a hernia defect. Gedney reasoned that if this approach worked on hernias, it should work elsewhere. He injected his unstable and feeble thumb, had a full recovery, and "prolo therapy" was born.

He spent the rest of life researching and forwarding prolotherapy for use in musculoskeletal pain, along with others. Prolotherapy has become more widely studied over the years and there is a database of medical literature available at www.prolotherapy.com and other websites. In 2005, the *Mayo Clinic Health Letter* reported: "In the case of chronic ligament or tendon pain that hasn't responded to more conservative treatments such as prescribed exercise and physical therapy, prolotherapy may be helpful."[28] Prolotherapy has been endorsed by former U.S. Surgeon General, C. Everett Koop,[29] and has also made its way into the professional sports world.[30]

Mechanism

Prolotherapy is based on the premise that chronic musculoskeletal pain is due to an inadequate repair of fibrous connective tissue, resulting in ligament or tendon weakness and relaxation (laxity),[31] also known as connective tissue insufficiency.[32] When connective tissue is weak, there is insufficient tensile strength or tightness,[33] resulting in excessive "loading" of the tissues that stimulate pain mechanoreceptors.[34] As long as connective tissue remains functionally insufficient or ineffective, these pain mechanoreceptors continue to fire with use, causing significant pain and limitation of function.[35] If the laxity or tensile strength deficit is not corrected sufficiently to stop pain mechanoreceptor stimulation, typically in the weeks to months after injury, chronic sprain/strain and pain results.[36] Prolotherapy works by stimulating a temporary, low-grade inflammation at the site of ligament or tendon weakness (fibro-osseous junction), "tricking" the body into initializing a new healing cycle cascade. Inflammation (characterized by increased blood flow) activates fibroblasts and native growth factors that stimulate the microenvironment to produce collagen, resulting in reinforcement of local connective tissue. This inflammatory stimulus effectively raises the level of various biochemical elements to resume or initiate a new connective tissue repair sequence to complete one that was prematurely aborted or never started.[37] Various proliferant solutions can be used in traditional prolotherapy; however, most common is dextrose, because it is safe yet still able to irritate tissues when concentrated.

Other ingredients used include sarapin, morruate, zinc, or other natural ingredients, combined with a local anesthetic. More recent formulas include platelet rich plasma (PRP), which contains growth factors, as well as bone marrow and adipose tissue, known to contain adult stem cells.

Approach to the Patient: Looking at the Big Picture

The body is an amazing system. An engineer will tell you the importance of understanding how one part of any system relates to the other. This concept is sometimes overlooked in traditional western medical models. In evaluating the patient for prolotherapy treatment, it is important that the physician understand how the system, which is now "malfunctioning," is operating as a whole. It is important to get an accurate history of the injury, when it began, what things have happened prior to and since it started, what makes it better, what makes it worse, and what treatments have been tried and their outcomes. Injuries and pain do not happen spontaneously or in a vacuum, although it may seem that way to the patient. Sometimes the diagnosis the patient gives you is not the actual cause of that person's pain. Also important to understand is that imaging studies such as MRIs can also be misleading with musculoskeletal pain[38,39] with false positives and negatives, so it is of primary importance that each physician fully evaluate the patient in front of them, correlate the physical findings, and not rely solely on imaging studies. To fully understand the importance of taking a good history, and looking at the system as a whole in the analysis of the patient, see Case Vignette 24.1.

Platelet-Rich Plasma Prolotherapy

Platelet-rich plasma is defined as autologous blood with concentrations of platelets above baseline levels, which contains at least seven growth factors.[40] Enhanced healing capability has been shown possible when platelet concentrations are increased within injured or damaged tissue.[41] In the 1990s platelet rich plasma (PRP) gained acceptance to accelerate healing in surgical circles; however, machines were large and expensive and, therefore, only used in hospital operating rooms. However, by the 2000s the size of the machines had diminished such that these were now portable and useable in an office setting. Prolotherapists, and other physicians in the orthopedic and sports medicine field began using platelet-rich plasma injections to stimulate musculoskeletal connective tissue repair. Platelet-rich plasma (PRP) prolotherapy is based

Case Vignette 24.1 Patient complaining of TMJ/jaw pain

36-year-old female, referred by her primary physician, with a request to receive prolotherapy for tempomandibular dyfunction and jaw pain. She said she had been clenching for several months and despite using a night guard had continued to have constant jaw pain. On taking a thorough history, the patient revealed her problems began with the initial onset of foot pain three years prior after regularly running on a treadmill. She saw a podiatrist who diagnosed a neuroma and injected cortisone with no change. She saw two other podiatrists who diagnosed her with plantar fasciitis and advised ice, massage, medication, and rest, which she did with no change. She continued to have foot pain then a few months later also began noticing bilateral hip pain. She was sent to an orthopedist who did MRI's and diagnosed bilateral labral tears, for which she eventually underwent arthroscopic hip surgery. The surgery helped only minimally, and she continued to have both the foot pain and the hip pain, and then also started having knee pain. A period of time after that the patient began to notice herself clenching, and started experiencing jaw pain. She was given a mouth guard, which did not help, and that was when she was sent for TMJ prolotherapy. Examination of the patient started at the feet. Ultrasound revealed a moderate plantar plate ligament tear. Her TMJ exam was unremarkable. After confirming the pain the patient was experiencing in her foot correlated to the ultrasound defect, she received four PRP prolotherapy treatments, spaced four weeks apart. The injections were done using ultrasound guidance to the plantar plate defect. After these treatments the patient reported improvement of her recalcitrant foot pain and dramatic reduction of her jaw clenching and pain; however, she was beginning to feel more pain in her hips and knees. She then received two PRP prolotherapy treatments for her hips and knees. This improved her pain overall in all areas with mild, residual foot pain. She eventually received one biocellular (adipose derived with PRP) prolotherapy treatment to her foot, and two months later ultrasound revealed complete resolution of her plantar defect. Her jaw pain had completely resolved, and she never needed injections there. Of note: jaw pain resolving without treatment points toward it being a compensatory pain, rather than a primary source. Once there is a correct diagnosis, and primary pain issue improves/resolves, compensatory issues will often also improve or resolve.

on the same theory and methodology as traditional dextrose prolotherapy; however, the solution used is a high-density concentration of the patient's circulating platelets, isolated and concentrated. Multiple reports and medical investigations, including double-blind studies, have validated the use of PRP in musculoskeletal healing.[42,43,44]

CONTRASTING THE ROLE OF DEXTROSE AND PRP PROLOTHERAPY

PRP prolotherapy and dextrose prolotherapy use similar techniques, and operate on the same theory of healing (Case Vignette 24.2). Both cause an irritation and stimulus that "tricks" the body into healing injured areas. Dextrose prolotherapy causes "growth-factor stimulation" because the irritation of the proliferant solution (dextrose) stimulates the influx of platelets, which then release growth factors.[45] However, in the case of PRP, platelets containing growth factors are directly injected into the injured tissue, making them immediately available. This can be more efficient; however, depending on the area and its condition, PRP may not be needed. Another difference is that with PRP prolotherapy, musculoskeletal ultrasound is often used both in diagnosis and guided injections, depending on the location, to help direct the PRP into areas of tissue deficit. This is less common when a practitioner is performing dextrose prolotherapy. However, PRP prolotherapy can be effectively used without ultrasound, as long as anatomical landmarks are well understood. PRP prolotherapy is usually preferred over dextrose prolotherapy when there is moderate to severe degenerative changes, such as osteoarthritis or tendonosis, or moderate ligament and tendon tear injuries, or where dextrose prolotherapy has failed.[46]

Biocellular Prolotherapy

The natural evolution of prolotherapy led to stem-cell sources for enhanced healing of connective tissue and joints for resolution of chronic musculoskeletal pain, especially where the problem was severe or more rapid healing was desired.[47] "Adult" stem cells are those cells present, which remain in an individual after birth in a partially undifferentiated state, and available to maintain tissue homeostasis and regeneration. However, if a joint area has been chronically injured and inflamed over a long period of time, a phenomenon called cellular depletion occurs. This means there are not very many local adult stem repair cells available; they have been used up over time. If cellular depletion has occurred, local repair stem cells will not be available or the available ones will be used up within a few treatments of dextrose and/or PRP prolotherapy. This is when biocellular prolotherapy is done, taking tissue from either the bone marrow or the adipose (fat) tissue, both known to contain adult stem cells, and using this as the "formula" to inject into the injury site.[48]

Attention to the important potentials of "adult" stem cells has been discussed in the medical literature since 1963 when Becker et al. reported on the

Case Vignette 24.2 Rotator-Cuff tear Treated with PRP Prolotherapy

A 40-year-old female hairdresser presented with a three-year history of right shoulder pain. She had seen three orthopedic surgeons with various diagnoses including lax capsule secondary to repetitive use, repetitive strain, thoracic outlet syndrome, and "nothing wrong." Cortisone, acupuncture, physical therapy, and NSAID medication were tried without any long-lasting result. Pain was "24/7" and described as a constant dull ache with some shooting "hot" pains with motion. She was unable to lie on her aggravated shoulder and frequently had disrupted sleep from pain. Her neck had begun to bother her, with muscle spasms, and her shoulder range of motion had decreased dramatically. Physical examination revealed shoulder abduction maximum 120° with "stickiness" indicative of adhesions, positive anterior compression test, along with decreased cervical range of motion and trapezius spasm. Musculoskeletal ultrasound revealed a subscapularis tendon intrasubstance partial-thickness tear and tendonosis, and supraspinatus articular surface partial thickness tear with calcific tendonosis (see Figure 24.1). Diagnosis was partial thickness rotator cuff tears and tendonosis (subscapularis, supraspinatus) and early adhesive capsulitis ("frozen shoulder") with compensatory cervicothoracic sprain/strain. This patient received an integrated approach of six PRP prolotherapy treatments to the rotator cuff, five dextrose prolotherapy treatments to the cervicothoracic spine (C5-T4), and four osteopathic manipulation (OMT) treatments, both for whole body alignment and to release shoulder adhesions. Treatment intervals were one to two months apart. At the end of the

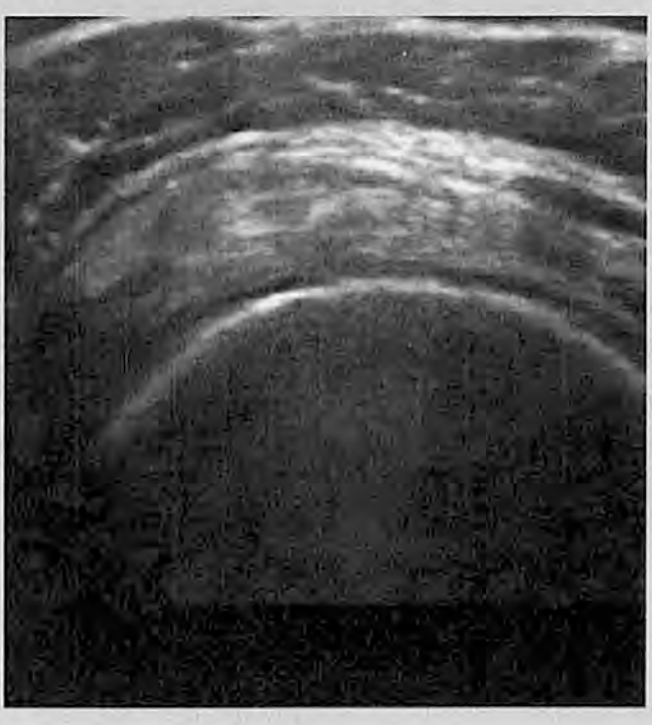

FIGURE 24.1. Before picture of supraspinatous tendon showing partial tear.

treatment course, the patient had 90% improvement with full range of motion and normal physical exam. Ultrasound evidence showed improvement of rotator cuff tendon tears and tendonosis (See Figure 24.2). The patient returned to work full time, and follow up at six months, one year and two years later showed continued improvement and stability.

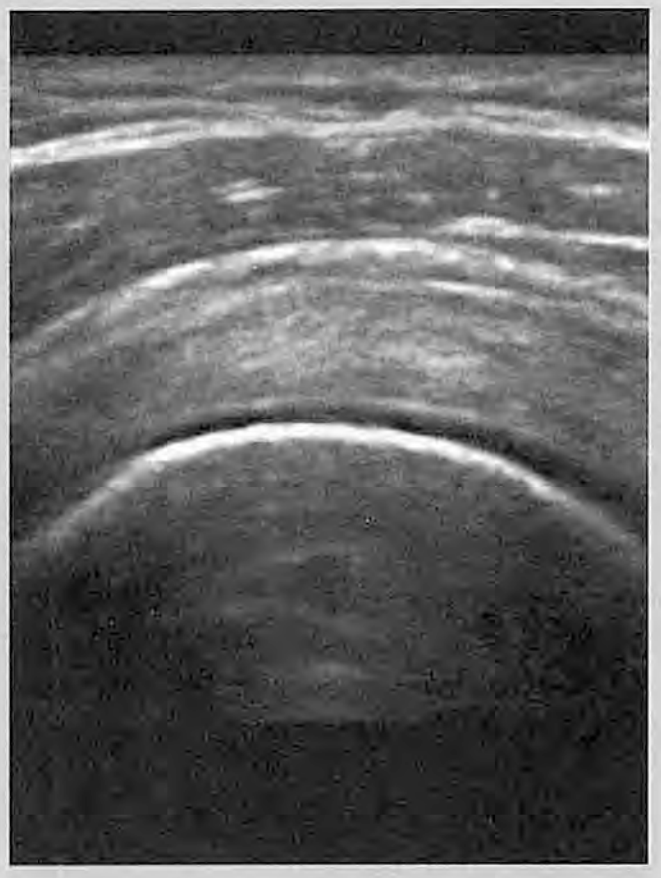

FIGURE 24.2. After image of supraspinatous tendon demonstrating improvement.

regenerative nature of bone marrow.[49] In the early 1990s, existence of adult mesenchymal stem cells, described as "noncommitted progenitor cells of musculoskeletal tissues," was discovered to have an active role in connective tissue repair.[50] These cells were first labeled by Caplan (1991) as "mesenchymal" stem cells ("MSC")[51] because of the ability to differentiate to lineages of mesenchymal tissue (which include ligament, tendon, cartilage), and were recognized to be an essential component of the tissue repair process. Of particular interest in musculoskeletal medicine is the observation in degenerative diseases, such as osteoarthritis, that an individual's adult stem-cell frequency and potency seems to be depleted, with reduced proliferative capacity and

ability to differentiate.[52,53,54] It has been suggested that addition of these missing stem-cell elements might help these conditions. Studies have demonstrated such improvement,[55,56] and MSCs have been noted to have the ability to "home in" and repair areas of tissue injury.[57]

Although bone marrow has historically been used as a source of MSC's, adipose-derived MSCs have been shown to have nearly identical capabilities.[58,59,60] Multiple human and animal investigations have clearly demonstrated the *in Vitro* ability of these cells to differentiate into and repair musculoskeletal connective tissues including ligament,[61] tendon,[62,63,64,65] cartilage,[66,67,68] disc,[69] muscle,[70,71,72] nerve tissue,[73,74,75] bone,[76,77,78] hematopoietic-supporting stroma,[79,80,81] and to actively participate in tissue homestasis, regeneration, and wound healing.[82, 83,84] There are different subtypes of biocellular prolotherapy: adipose derived with PRP, adipose derived with bone marrow aspirate concentrate ("BMAC"), and BMAC alone. The decision of which subtype to use is based on the particular location and severity of the problem.

Patient Selection

In the 1950 publication of the Hackett/Hemwall/Montgomery book on Prolotherapy, one of the first actual texts on the subject, the authors provided criteria for patient selection as noted in Box 24.1.

These criteria are still true today whether the person is receiving dextrose, PRP, or biocellular prolotherapy. The problem must be an appropriate musculoskeletal problem; the patient needs to have the desire to get better; no known illness that could prevent healing; willingness to follow instructions; and, of course, to receive injections. Also, the patient should not be taking drugs,

Box 24.1 Criteria for Injection Therapy in New Patients

- Appropriate medical problem.
- Desire for recovery.
- No underlying medical conditions that would significantly interfere with healing.
- Ability and willingness to follow instructions.
- Willingness to report progress.
- Willingness to receive painful injections in an effort to recover from injury.

For further reading, see Hackett GS, Hemwall GA, Montgomery GA. *Ligament and Tendon Relaxation Treated by Prolotherapy*. (1956 First Edition Charles C. Thomas), Fifth Edition Gustav A. Hemwall, Institute in Basic Life Principles, Oak Brook, IL, 1991.

which lower the immune system such as systemic corticosteroids or immune suppressants. Age is not a factor, and it does not matter how long the person has been in pain or how long ago the injury occurred, as long as the person is in good general health. Because prolotherapy works to stimulate inflammation, patients should not be taking anti-inflammatory medication during treatment. In fact, although frequently prescribed for musculoskeletal pain, use of NSAIDs may interfere with healing and is questionable in treatment of musculoskeletal injuries.[85]

Typical Treatment Course

Every individual is different, and although there are treatment guidelines, the plan should be customized by the physician to the individual patient. For dextrose and PRP prolotherapy, an average of four to six total treatments is spaced at four to six week intervals, each treatment involving multiple injections to a particular area. For biocellular prolotherapy the interval is usually longer, approximately six to twelve months between treatments, and sometimes augmented with one or two PRPs before or after a biocellular treatment. Typically the practitioner will start with the least invasive form of prolotherapy which is expected to work, and advance as needed. The algorithm for incorporation of prolotherapy is noted in Figure 24.3.

Conclusion

Chronic musculoskeletal pain is prevalent in our society; however, there is controversy about the effectiveness of traditional treatment options. An integrative approach is valuable in these cases. Prolotherapy offers a minimally invasive, low-risk option that has a high success rate for appropriate problems. Newer forms of prolotherapy, such as platelet-rich plasma and biocellular (stem-cell) prolotherapy offer an ability to accelerate healing for difficult problems, and more options for the patient in pain.

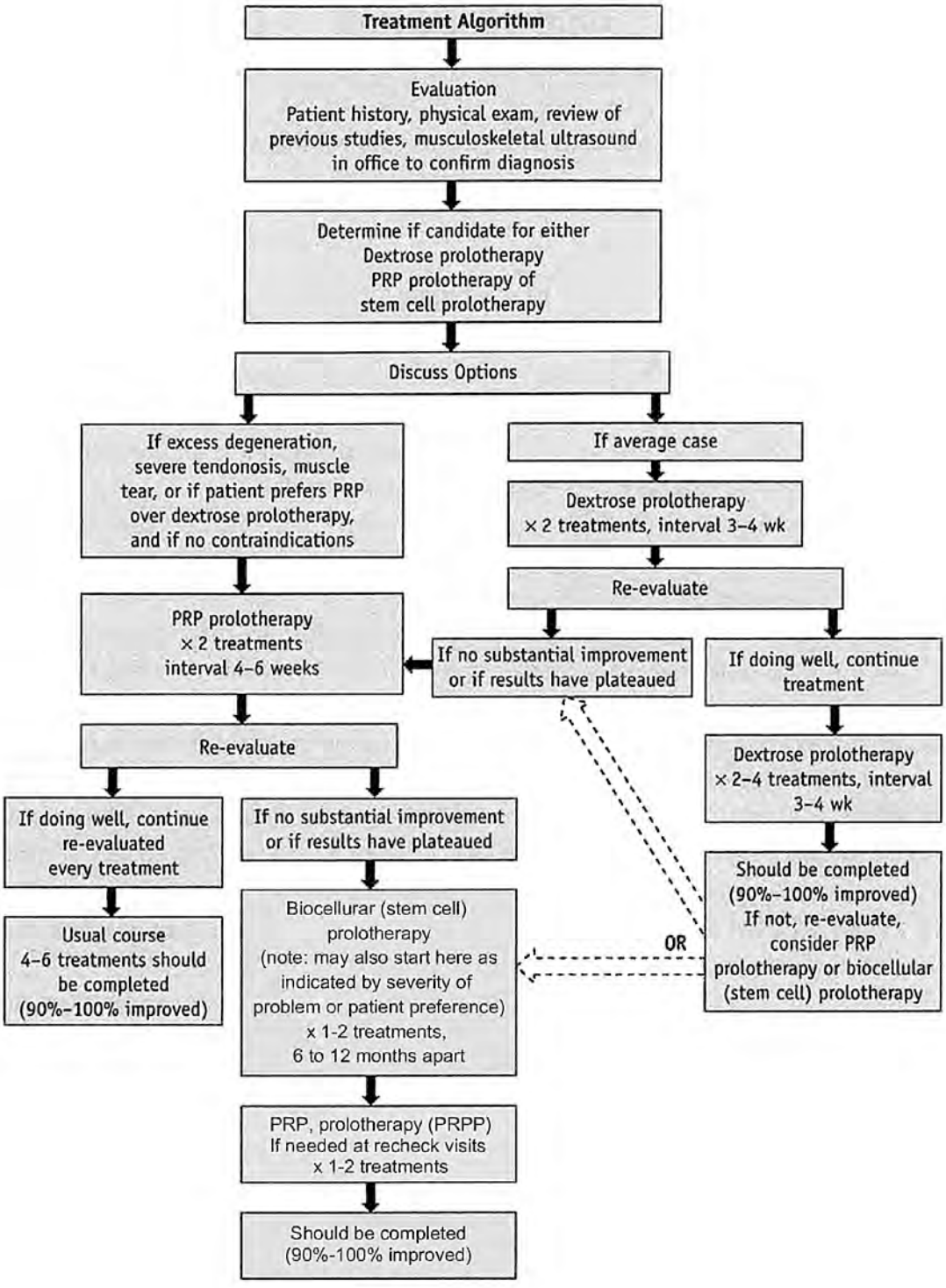

FIGURE 24.3. Treatment Algorithm.

Online Resources

- The American Association of Orthopaedic Medicine (AAOM):
  - http://www.aaomed.org/prolotherapy

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