Research and Reports in Urology

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Peyronie's Disease: An Outcomes-Based Guide to Non-Surgical and Novel Treatment Modalities

Amit G Reddy, Michelle C Dai, Jeffrey J Song, Hudson M Pierce, Sagar R Patel, Larry I Lipshultz

Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA

Correspondence: Larry I Lipshultz, Scott Department of Urology, Baylor College of Medicine, 7200 Cambridge Street, Suite 10B, Houston, TX, 77030, USA, Tel +1 713 798-6270, Fax +1 713 798-6007, Email larryl@bcm.edu

Abstract: The clinical landscape of Peyronie's disease is everchanging. There has been growing interest in non-invasive therapeutic options that could assist patients with achieving a meaningful reduction in penile curvature without surgical intervention. These therapies are wide-ranging in terms of their mechanisms of action, efficacies, and short- and long-term safety profiles. Recently, an abundance of outcomes literature on longstanding and novel non-surgical treatment modalities has been published. For sexual medicine providers hoping to offer patients the most up-to-date and evidence-based treatments for the management of Peyronie's disease, it can be challenging to gain a thorough understanding of this body of literature. In this clinical management review, the workup and current theories on the pathophysiology of Peyronie's disease are reviewed, and the most recent outcomes data on the currently available non-surgical treatment modalities are presented. With an accurate understanding of the current landscape of Peyronie's disease treatment, sexual health providers will be able to better evaluate and engage in evidence-based shared decision-making with their patients.

Keywords: Peyronie's disease, shockwave therapy, platelet rich plasma, Xiaflex, penile curvature, antioxidant therapy

Introduction

Peyronie's disease (PD) remains one of the most challenging and poorly understood disease processes in sexual medicine. First described as early as the 1600s in Dutch case reports, the formal recognition and popularization of the condition did not occur until 1743, when François Gigot de LaPeyronie characterized a patient whose penis was filled with scar tissue and an upward curvature.[1] At present, PD is estimated to impact between 0.3% and 13.1% of men worldwide.[2] However, given the stigma associated with the condition, there is likely some degree of underreporting and thus, underestimation of the true prevalence of PD. From a financial perspective, a recent analysis investigating treatment costs of PD found that individual costs increased from $1531 in 2007, to $10,339 in 2018, largely attributed to the increased prevalence of injectable medications.[3] Given the expanding landscape of PD management, it is paramount for providers to remain updated regarding the specific indications and efficacies of the standard and novel treatment options available. By doing so, physicians can help patients make an informed and shared decision regarding treatment modality selection. The aim of this clinical review is to present a comprehensive overview of non-surgical and novel treatment modalities for PD while underscoring treatment outcomes, safety, and efficacy.

The Stages of Peyronie's Disease

PD can be divided into an acute and stable phase. In the acute phase, inflammation of the tunica albuginea frequently occurs after clinical or subclinical penile trauma. At this point, penile plaque formation begins, and these changes collectively reduce the elasticity of the tunica albuginea and contribute to the formation of a rigid penile plaque. The acute phase can last up to 18 months, and patients commonly exhibit penile curvature, pain, and loss of length.[4–6] During the stable phase, pain subsides and the plaque become even more organized; eventually, no further progression in plaque size or penile curvature occurs. While penile trauma is the most cited risk factor for PD, not all patients present with

Received: 4 October 2022
Accepted: 11 January 2023
Published: 2 February 2023

a history of trauma. Additional risk factors that have been associated with the development of PD include diabetes mellitus, transurethral procedures, hypertension, Dupuytren's contracture, smoking, and alcohol consumption.[7–9] The role of testosterone in wound healing has also been explored in relation to PD, as hypogonadism is also believed to have a potentially contributory effect on its development.[10] Additionally, recent literature supports an increased prevalence of low testosterone levels in PD patients.[11] While the exact etiology of PD remains unknown, many believe that it is a multifactorial process. In recent years, research efforts exploring the progression and underlying architecture of Peyronie's plaques have facilitated advancements in medical therapy for this population.

Pathophysiology of Peyronie's Plaque Formation

The tunica albuginea consists of an irregular lattice of elastic fibers with dispersed type 1 collagen fibers. The surrounding vasculature is arranged such that the arteries are supported by areolar tissue, while veins directly contact the tunica albuginea. Non-traumatic mediators of inflammatory processes within this fibrous structure are unknown but may be associated with previously stated risk factors. Penile trauma and microtrauma are hypothesized to induce extravasation of blood and cellular infiltrates.[12,13] These processes compress nearby venous structures and promote edema and a prolonged inflammatory phase. They can also sensitize and damage nerve endings, which is one theory for the pain associated with the acute phase. Prolonged inflammation results in a similarly prolonged and unregulated wound healing process, inducing continued fibrin deposition, deposition of collagen fibers, and elastin breakdown within the tunica albuginea.[14]

Transforming growth factor ß1 (TGF-ß1), plasminogen activator inhibitor 1 (PAI-1), interleukin-1 (IL-1), IL-6, and reactive oxygen species (ROS) have additionally been implicated in promoting a pro-fibrotic environment to support fibroblast proliferation.[14–16] TGF-ß1 most notably stimulates fibroblast recruitment and myofibroblast proliferation, resulting in collagen deposition. Myofibroblasts and TGF-ß1 act together to inhibit lysis of fibrin and collagen by further promoting extracellular matrix (ECM) deposition and inhibiting ECM turnover. Normal wound healing is balanced by the action of matrix metalloproteinases (MMPs). In PD, MMPs are not significantly activated, while tissue inhibitors of MMPS (TIMPs) are activated, thus promoting unregulated ECM deposition.[1,2,16,17] ROS are released by distressed cells, macrophages, and neutrophils through oxidative burst. Production of the above inflammatory factors and ROS additionally promotes NF-κB activation, propagating further release of inflammatory cytokines.[18] Platelet-derived growth factor (PDGF) has also been implicated in ECM deposition and fibrotic plaque formation. PDGF is secreted by platelets, endothelial cells, and macrophages in response to trauma and further upregulates TGF-ß1, myofibroblasts, and fibrotic cells.[19] Immunohistochemistry (IHC) stains and Western blot assays additionally reveal elevated levels of α-actin, ß-catenin, and heat shock protein 47 (HSP-47), a collagen-specific chaperone. These elevations further support a pro-inflammatory state and may contribute to contracture and subsequent penile curvature.[20] Collectively, an inflammatory cascade is triggered, which propagates fibrosis and plaque formation over fibrinolysis and plaque degradation.

The three primary histologic patterns of plaques are dense fibrotic plaques, dense fibrotic plaques with focal or patchy metaplastic ossification, or plaques with predominant metaplastic ossification. The fibrotic components of plaques are largely hyalinized or lamellar in structure.[21] Plaques exhibit abnormal elastin and fibrin structural organization with elevated levels of collagen I and III.[22–25] PD plaques additionally expressed elevated collagen III/I ratios in rat models of chronic PD.[23] The above pathological factors persist within the plaques themselves to support plaque integrity into the stable phase.[17] PD plaques exhibit normal levels of hyaluronic acid and dermatan sulfate but elevated levels of chondroitin sulfate (CS).[16] CS is a glycosaminoglycan and acts as a primary building block of human cartilage. Analysis of mineralized plaques shows elevated counts of calcium (Ca) and phosphorus (P) with a Ca/P ratio similar to that of bone. Zinc (Zn) counts were additionally elevated and have been implicated in both MMP and NF-κB pathways. Further, dentin matrix protein-1 (DMP-1) was colocalized in a proteoglycan- and collagen-rich matrix that contained osteocytic lacuna-like features.[24] Calcification of plaques can be partially attributed to upregulation of pleiotrophin (PTN) and action of TGF-ß1. PTN is a growth factor that promotes osteogenesis and proliferation of fibroblasts and osteoblasts. TGF-ß1 additionally promotes differentiation into an osteogenic cell line.[25,26] In all, these findings support the gradual conversion of PD plaques from a fibrous morphology to one that increasingly resembles bone.

Workup

To make a diagnosis of PD, clinicians should obtain a detailed history that includes any potential risk factors for plaque formation and perform a detailed and focused genitourinary exam. Recommendations for use of penile duplex ultrasound vary, and laboratory testing is not indicated for diagnosing PD.[27]

A detailed history and symptomatology can help determine whether the patient's PD is in the acute or stable phase. This distinction is very important, as treatment plans differ significantly depending on the phase of PD. Important features to note during the clinical encounter include onset and duration of symptoms, pain with erections, palpable nodules, degree of curvature, whether symptoms and deformities are progressive or stable, and alterations in length, girth, or erectile function.[28] In the acute phase, patients commonly – but not always – present with penile pain and penile curvature. While plaques begin to form during the acute phase, lesions may not be clearly palpable, and patients may not be immediately aware of their presence. Erectile dysfunction (ED) may additionally develop in the acute phase and persist into the stable phase. The stable phase is commonly associated with resolution of prior penile pain and stabilization of curvature.[6]

PD can additionally be psychosocially taxing for patients. As such, psychiatric history and impact on relationships should also be elicited in the medical history. Two questionnaires are often used with patients presenting for PD. First, the Peyronie's Disease Questionnaire (PDQ) is a 15-question survey validated for the evaluation and quantification of the impact and severity of PD symptoms across 3 domains: psychological and physical symptoms, penile pain, and symptom bother.[7] Second, the Sexual Health Inventory for Men (SHIM) questionnaire is often concurrently given to patients with PD who may have concomitant ED. The SHIM questionnaire is a 5-question survey validated for the evaluation of erectile function.[29]

Physical exam of the penis in both the flaccid and erect states provides valuable insights into the physical manifestations of PD. In the flaccid state, important features to note include plaque location, size, and length. Stretching the penile shaft can assess erectile tissue health as significant corporal fibrosis impairs shaft elasticity.[2] In the erect state, important features to note include penile length and girth, direction and degree of curvature, shape of penis, any hourglass deformity, and point of maximum curvature. Of note, patients tend to overestimate their actual degree of curvature by an average of 20 degrees.[30] Given that PD has been associated with fibrosis of the palmar and plantar fascia, known as Dupuytren's contracture and Ledderhose disease, respectively, patients should be assessed for these conditions and given prompt referrals to specialists when indicated.[31]

Evaluation of the erect penis can be done in-office with intracavernosal injections (ICI). Supplementation with penile duplex ultrasound can provide information on plaque size, location, and calcification.[32] The American Urological Association (AUA) recommends use of duplex ultrasound prior to any invasive interventions.[27] Magnetic resonance imaging (MRI) can also be used to detect plaques and inflammation but is currently not recommended for routine use.[33]

Laboratory testing is not indicated for diagnosing PD given that no specific markers for PD have been identified. However, testing for common comorbidities may be beneficial in identifying any potential risk factors and establishing adjuvant treatments for them.

The primary differential diagnosis according to the AUA guidelines is fairly limited: congenital penile curvature, thrombosed or torn dorsal penile vein, penile fracture, and cancer. Congenital penile curvature should be suspected with a young patient presenting with lifelong ventral curvature without pain or penile plaque. Unlike PD, this condition is not the result of excess fibrosis and scarring. Thrombosed or torn dorsal penile vein and penile fracture both present with acute penile ecchymosis, pain, and swelling. These conditions present very swiftly, whereas PD presents more sub-acutely on the order of weeks to months.

Finally, it is important to note that currently, the only guideline recommended treatment option for acute phase PD is non-steroidal anti-inflammatory drugs (NSAIDs), which are intended to treat pain associated with the condition.[27] The treatment modalities listed in this review are generally recommended for the treatment of stable phase PD and as such, any reference to PD in the following sections refers to stable PD unless otherwise specified.

Oral Therapies for Peyronie's Disease

At present, the AUA does not recommend any oral therapy in the treatment of PD.[27] While numerous studies have been reported in the literature, the quality of these data and the reporting of safety and efficacy outcomes have been very heterogeneous. Thus, the authors felt that reporting on these therapies was outside the scope of this clinical management review.

Vacuum Erection and Penile Traction Therapy

Vacuum Erection Devices

For patients with PD who are seeking non-invasive treatment options, vacuum erection devices (VED) may be a potential option with a limited risk profile. VED uses negative pressure to enhance arterial inflow and a constriction band to mechanically limit venous return, thereby improving oxygenation of the corpora and dilating the cavernous sinuses.[34] While it is commonly believed that this molecular environment promotes tissue healing and repair as evidenced by VED usage for post-prostatectomy ED patients, there has been limited investigation about whether similar benefits can be seen for PD. Of note, TGF-ß1 is believed to also be downregulated with VED usage.[35] Furthermore, based on the data from traction therapy and manual modelling done at the time of inflatable penile prosthesis(IPP) placement, there is some thought that regular, mechanical stretching of the penis may cause plaque microtrauma and remodeling to a lesser angle of curvature.[36,37]

While a limited number of studies have been published assessing VED as a treatment option for PD, most of these trials utilized VED as part of a combination therapy, thus making it challenging to understand just how much of a role VED played in treatment outcomes. Recently, MacDonald et al published a study that evaluated 53 treatment naïve patients with PD, of whom 20 chose VED therapy (10 minutes, twice daily) and 33 that chose no intervention.[38] There were no significant differences in age, duration of PD, degree of curvature, or comorbidities between the two groups. While both groups demonstrated significant improvements in curvature, there was a 5-fold improvement in penile curvature in the VED group compared to the control group (23°, $p = 2.6\times10-6$ vs 3.6°, $p = 0.048$, respectively). Additionally, the VED group demonstrated non-significant improvements in SHIM scores, while the untreated group had reductions in their SHIM scores. Penile pain or length were not outcomes assessed in this study. In 2010, Raheem et al published a similar study utilizing VED monotherapy (10 minutes, twice daily) for 12 weeks and noted statistically significant improvements in penile length, pain, and curvature, with 67.7% of patients reporting a reduction in curvature of 5 to 25 degrees.[39] Approximately half the patients were satisfied with their outcome and pursued no further intervention, while half pursued surgical intervention. With regard to adverse outcomes, when used as prescribed, VED is considered a generally safe form of therapy with the most common side effects being hematoma formation and painful venous engorgement.[40]

Although limited, the current data indicate some role for VED therapy in select PD patients. Nevertheless, it is important to note some of the challenges with achieving maximal VED efficacy, which include patient compliance and appropriate usage of the device. Future randomized control trials (RCT) should identify patient factors that improve VED outcomes, methods to improve device compliance, and standardized treatment protocols that are easy to replicate. Moreover, since VED is often utilized as part of combination therapy, RCTs that evaluate its role as an adjunctive therapy are necessary. Finally, given that multiple types of VEDs are in the market, it is often challenging to accurately compare trials utilizing different types of devices.

Penile Traction Therapy

One of the mainstays of conservative PD treatment is penile traction therapy (PTT). Though first published by Levine et al in 2008, there have been numerous iterations of PTT devices and techniques since.[36] Similar to VED, PTT has been utilized as monotherapy or in conjunction with other treatments such as intralesional injections and surgery.[41] In one of the largest series of PTT monotherapy to date, Moncada et al reported on 80 stable phase PD patients who underwent PTT utilizing the PeniMaster Pro device (MSC Concept, Berlin, Germany) and compared them to a group of non-intervention patients[42]. PTT patients were instructed to utilize the device for 3–8 hours daily, with gradual increases in

the amount of force applied. Of the 41 patients in the treatment arm, there was a statistically significant improvement in mean curvature, and this change directly correlated with the amount of daily traction time undertaken (PTT < 4 hours/day – mean curvature reduction 19.7°; P < 0.05, PTT > 6 hours/day – mean curvature reduction 38.4°; P < 0.001). In addition, penile length also significantly increased in the treatment group compared to baseline (+1.8 cm; P < 0.05) and improvements in International Index of Erectile Function (IIEF) scores were noted. In comparison, no changes were noted in the non-intervention arm.

Recently, a novel form of PTT, known as RestoreX© (PathRight Medical Inc, Plymouth, MN, USA) was introduced by urologists at the Mayo Clinic. In the initial RCT, cohorts were matched for age, duration of disease, and curvature. The PTT group was instructed to utilize the device for 30–90 minutes daily, and at the three-month follow-up, significant improvements in penile length (0.5 cm vs 0 cm, p < 0.001), curvature (−11.7° vs 1.3°, p < 0.01) and IIEF scores (4.3 vs −0.7, p = 0.01) were noted in comparison to control.[43] These improvements were also noted at the 6- and 9- month follow-up intervals. This was a significant improvement for PTT given that the daily duration of traction therapy necessary to achieve improvements in curvature was significantly less than prior regimens. Moreover, given that longer duration of device usage was a previously noted reason for poor compliance, the condensed duration of treatment would likely also translate to improved compliance rates with this modality of therapy.

Although one of the major limitations of the PD literature is the paucity of long-term outcomes data, Capoccia et al recently reported on 88 patients who elected for conservative therapy for their PD and reported that of all the conservative options including oral and topical therapies, only PTT was noted to be associated with statistically significant improvements in patient reported changes in penile curvature, penile length, and the ability to engage in penetrative intercourse.[44] While this data is subjective in nature, it does provide some longitudinal insight into PTT outcomes and can serve as a decision aid for patients interested in non-surgical options.

Across the majority of PTT trials and regardless of the type of device utilized, PTT monotherapy was not found to have any significant adverse effects.[45] Similar to the VED data, the literature on PTT therapy is very heterogeneous regarding types of traction devices used, timing of intervention during acute versus stable phase, and even duration of therapy amongst other patient factors. For these reasons, drawing comparisons and conclusions from these studies is challenging as the data cannot be analyzed using any type of pooled statistical analysis. More RCT data with standardized devices and treatment protocols will be key to drawing more accurate conclusions on the safety and efficacy of PTT.

Intralesional Injection Therapies

Collagenase Clostridium histolyticum

Intralesional collagenase clostridium histolyticum (CCH; Xiaflex®) remains the only Food and Drug Administration (FDA) approved intralesional therapy for PD.[46] This class of enzymes is believed to work on PD plaques by hydrolyzing collagen fibers and downregulating extracellular matrix-associated genes, cytokines, and growth factors, to collectively break down existing plaques and suppress new plaque formation.[47] The first two landmark RCTs for CCH, Investigation for maximal Peyronie's reduction efficacy and safety studies (IMPRESS) I and II, compared intralesional CCH to intralesional saline.[48] Significant improvements in percent change of penile curvature (34% vs 18%, respectively) and mean PD symptom bother score (−2.8 vs −1.8, respectively) were found in the treatment group in comparison to placebo. Goldstein et al collected and analyzed 5-year outcome information from patients previously enrolled in IMPRESS I and II, as well as two additional open-label studies.[49] They found an additional 9% decrease in curvature as well as a decreased PDQ bother score, five years after initial treatment.[8] Although subsequent study designs have varied, multiple studies have demonstrated an improvement in the degree of curvature ranging from 13° to 23°.[50,56] Most recently, a 2022 meta-analysis found an average improvement in curvature of approximately 19° more than that of placebo.[57] Besides these objective measures of improvement, CCH also has been demonstrated to consistently improve PDQ and IIEF scores.[48,51,54,56]

A pooled safety analysis of six studies done in 2015 found that 86% of CCH patients had at least one treatment-related side effect.[58] However, they were most often minor, including ecchymosis, swelling, mild hematoma, and pain.

Serious complications such as corporal rupture were rare, occurring in just 0.7% of patients in the IMPRESS studies and 0.9% of patients in the pooled safety analysis.[58,59] Only acute adverse effects and no long-term effects were identified in the 5-year follow-up studies of the IMPRESS trials.[49] Of note, CCH did not cause significant penile shortening, a common complication of surgical treatment for PD.[48,60–62]

Several recent studies aimed to identify candidates most likely to respond to CCH, but reports vary regarding clinical and demographic factors associated with improved outcomes. Many studies have found that a greater degree of plaque calcification is associated with less curvature reduction with CCH.[49,59,63,64] However, other studies did not find an association between calcification and treatment response.[50,65,66] Likewise, while longer duration of disease (>4 years) in the IMPRESS trial was associated with greater percentage improvements in penile curvature (− 40° vs − 14°) and PD bother scores (− 3.0 vs − 1.6), later studies did not corroborate these findings.[50,54,59,63]

Overall, at present, there is conflicting data on how certain clinical factors such as duration of PD, initial degree of curvature, and plaque location impact outcomes of CCH therapy. More research is needed to better understand the role of these clinical and demographic factors.

Verapamil

Another intralesional therapy that has previously been utilized in the treatment of PD is verapamil injections. In rat models, intralesional verapamil injections were noted to decrease collagen and elastin fibers on IHC staining when compared to intralesional saline injections.[67]

Intralesional verapamil injection into males was first reported in 1994 by Levine et al in a nonrandomized, preliminary study of 14 men who received biweekly injections for six months. There was a subjective improvement in curvature in 42% of subjects.[68] Later research by Levine et al found that of 140 patients who completed intralesional verapamil therapy, 60% had a measurable decrease in curvature. A majority of subjects also reported subjective increases in girth (83%) and in sexual function (71%).[69]

However, multiple subsequent RCTs that enrolled between 14 and 80 subjects showed no significant improvement in penile curvature with intralesional verapamil compared to saline injections.[70–72] Furthermore, electromotive administration of verapamil was not associated with improvement in curvature when compared to electromotive administration of saline in a double-blind RCT of 42 men and is not recommended as a treatment option by the AUA PD guidelines.[73]

Because of the limited positive outcomes data and availability of other proven intralesional therapeutic options, the AUA clinical guidelines on PD recommend that physicians carefully consider whether verapamil injections are appropriate before initiating treatment.[27]

Interferon

Interferon- α2b (IFN) is a naturally-occurring cytokine that inhibits fibroblast proliferation and collagen production in vitro.[74] In 2006, a placebo-controlled parallel study of 103 men with noncalcified plaques found that biweekly intralesional injections of IFN for 12 weeks was associated with significantly greater decrease in penile curvature (14°), decrease in plaque size and density, and pain resolution compared to intralesional saline.[75] In support, other retrospective cohort studies also demonstrated a similar decrease in mean penile curvature from baseline.[76,77] Most recently, a prospective study of 86 patients with noncalcified plaques found that after three months of treatment, there were significant decreases in mean penile curvature (16°), mean plaque volume (225 mm^3), mean visual analogue scale (VAS) scores (3 points), and IIEF scores (7 points) at 3-month follow-up.[78]

While intralesional IFN is considerably cheaper than CCH, a retrospective study of 346 patients found that CCH injections had an approximately two-fold improvement in curvature compared to IFN injections in a head-to-head comparison (19 ° vs 9°). Additionally, the CCH patients were 1.5x more likely to experience ≥20% improvement in curvature (71% vs 47%).[79]

There is limited evaluation of demographic and clinical factors associated with improved response to intralesional IFN. A retrospective review of 131 patients who received a median of 12 IFN injections found no difference in improvement in penile curvature between ventral and dorsal plaques.[77] History of genital trauma may be a pre-procedural factor associated with improvement in penile curvature for intralesional IFN therapy.[77] Another study on

IFN use found no difference in treatment response when comparing for age, tobacco use, history of diabetes, location of plaque, or initial IEEF-5 scores.[76] A minor curvature (<30°) was associated with a higher likelihood of achieving ≥20% improvement, but not a greater absolute curvature improvement.[76]

The side effects of IFN are mild to moderate and consist of flu-like symptoms such as nausea, weakness, fever, and rashes.[75,80] A study comparing IFN to tunical plication found that IFN resulted in preserved or improved erect penile length in 67% of patients compared to 14% of patients who received tunical plication ($p = 0.005$).[61] Thus, another role for IFN and other intralesional injection therapies may be for those patients who prioritize penile length, although much more data are necessary before such conclusions can definitively be made.

Novel Therapies for Peyronie's Disease

Extracorporeal Shockwave Therapy

More recently, low-intensity extracorporeal shockwave therapy (LiESWT) has gained attention as a non-invasive treatment modality for a variety of pathologies. While initially utilized for the management of soft-tissue pathologies such as plantar fasciitis and tendinopathies, the indications for its use have expanded in recent years, including into urologic pathology.[81,82] Specifically, LiESWT has been cited as a potential, novel treatment option for ED.[83] In 2021, Ortac et al published a prospective, placebo-controlled single-blinded trial of 66 patients with mild ED who underwent LiESWT therapy.[84] The group found a statistically significant improvement in the IIEF scores of the treatment arm at 3- and 6-month follow-ups, along with a statistically significant improvement in the ability to successfully penetrate for intercourse. Unfortunately, the majority of data on the safety and efficacy of LiESWT for urologic indications has been in the form of single-center retrospective and prospective studies that are non-placebo controlled. This also holds true for the data on LiESWT for the treatment of PD.

In 2019, Mauro et al published a single-arm observational study of 325 treatment naïve men with PD who underwent once weekly LiESWT for six weeks, and assessed changes in penile curvature, plaque size, and sexual function in patients.[85] The group reported statistically significant reductions in degree of curvature (30.4° vs 25.0°), plaque size (1.78 vs 1.53 cm), and PD associated pain, along with increases in penile length and improvements in IIEF scores at 3-month follow-up ($P < 0.001$). More recently, Bakr et al published a meta-analysis looking at RCT data on the treatment of PD.[86] Only three RCT studies of LiESWT between the years 2000–2020 were identified and the analysis failed to find any improvements in penile curvature or pain within the overall cohort. While some improvements in plaque size were noted, the clinical significance of this finding is uncertain as curvature and pain are often the most bothersome symptoms. Most recently, Abdesseater et al performed a retrospective analysis of 39 men with acute-phase PD and curvature <40 degrees, who underwent LiESWT (six weekly sessions of 4000 pulses each) for an average of 7.2 sessions.[87] A statistically significant improvement in pain scores was noted, but not in plaque size or curvature. Interestingly, on multivariate analysis, the predictors of success were noted to be younger age and concurrent use of PDE-5 inhibitors.

Based on these findings, at present, the use of LiESWT for the treatment of PD can only be described as a safe, non-invasive, and experimental therapeutic option. Given the variability in treatment protocols, follow-up intervals, patient populations, and relatively minimal RCT data, it is challenging to conclusively state whether LiESWT is an effective treatment for PD with regard to changes in penile curvature, length, or plaque size. In addition, minimal data on the most effective treatment protocols or factors influencing patient success exist. At present, the AUA guidelines only recommend the use of LiESWT for PD associated pain.[27] Thus, for those providers who choose to incorporate LiESWT into their treatment algorithm for PD, it would be prudent for them to educate patients about the currently available outcomes data and thereby set realistic expectations.

Platelet Rich Plasma

Another novel treatment option that has gained more attention recently is the use of platelet-rich plasma (PRP) in the treatment of urologic pathology. PRP had previously been utilized as a regenerative therapeutic option for orthopedic and dermatologic pathologies, but recent studies have investigated its potential role as a treatment for ED and PD.[88] In a recent double-blinded and placebo-controlled clinical trial utilizing PRP for the treatment of ED, researchers found

improvements in IIEF scores at multiple time points up to six months in comparison to placebo.[89] In the study, a washout period was conducted for men on phosphodiesterase type 5 inhibitor (PDE5i) therapy and men between 40 and 70 years of age with mild-to-moderate ED were the target population. While the study excluded men with a history of PD to limit confounding variables, it is known that many men with PD also suffer from concurrent ED, which is why a potential therapeutic option that can treat both pathologies would be extremely beneficial.

At present, the utilization of PRP for the treatment of PD remains an area of limited understanding. PRP is believed to exert regenerative effects at sites of tissue injury by releasing various cytokines and growth factors that promote angiogenesis and connective tissue regrowth.[90] This is believed to be mediated by a supratherapeutic concentration of platelets within the sampled plasma, which release these growth factors and accelerate tissue healing. However, in the case of PD, it is unclear how exactly this mechanism of action would alter plaque size and curvature. Notsek et al administered intralesional PRP to 32 patients with PD, and normal saline to 27 patients with PD.[91] At six months, the curvature angle decreased by 50% and 22.2%, respectively, the plaque size decreased by 50% and 14%, respectively, and IIEF scores improved by 56.3% and 3.7%, respectively. While these findings were statistically significant, trauma from the needling alone provided some therapeutic benefits, as evidenced by the improvements seen in the placebo arm. This indicates that the improvements noted in the treatment arm may not solely be a direct result of PRP alone and that the injection process itself could be causing disruption of plaque microarchitecture, a phenomenon that has been previously reported in the ICI literature.[48]

In an effort to further optimize PRP therapy, Matz et al converted PRP to platelet rich fibrin matrix (PFRM), a fibrin matrix that would ideally attach to platelets and prevent their extravasation away from the target site, thereby increasing the duration of action and potentially improving treatment outcomes.[92] A total of 11 PD patients were included in the study, and each received a total of 2.1 injections on average. IIEF scores were reported to have improved by 4.14 points in the groups with ED and PD, and up to 80% of PD patients reported subjective improvements in their curvature. While these outcomes are subjective at best, the study does highlight a method to potentially augment PRP effectiveness, and future prospective trials with more defined outcomes may delineate if PFRM is a more effective method of PRP therapy. Virag et al combined PRP with hyaluronic acid (HA) in 75 PD patients and administered a total of six rounds of ultrasound guided intralesional plaque therapy.[93] In these patients, a statistically significant decrease in angulation and plaque thickness was observed. In addition, in the 22 patients with concomitant ED, approximately 1/3 of patients reported an improvement in IIEF scores (no statistical data reported). However, it should be noted that some of these results were not as significant in patients with more severe disease (eg angulation >60 degrees and calcified plaques).

Similar to Li-ESWT, one of the main challenges with interpreting the data surrounding PRP is the wide variability in study designs, patient populations, and treatment protocols within the currently available literature. At present, many questions remain unanswered including (1) whether PRP therapy during the active phase or stable phase has superior outcomes, (2) the ideal dosage or duration of treatment, (3) whether intralesional PRP can also concurrently improve EF, and (4) defining the long-term safety and efficacy of PRP. In addition, as previously noted, many patient-specific factors, such as the severity of curvature and presence of calcifications within the plaque, will also need to be included in future studies so that patients with these conditions can be appropriately counseled on how their specific disease burden may respond to therapy. Moreover, given that autologous PRP is currently the most commonly utilized approach to administration, it should be noted that there is some recent data to suggest that growth factor concentration can vary among men with ED.[94] This data could suggest that not all patients may achieve the same benefits from their own PRP and that more research into what patient factors may potentiate or impair PRP response will also be important to optimize patient selection and treatment efficacy. A recent systematic review concluded that currently there is not enough data to suggest that PRP improves PD significantly enough to achieve easier sexual penetration.[95] However, as previously noted, research into the various aspects of PRP delivery and patient selection may help to improve future outcomes and deliver clinically meaningful results.

Combination Antioxidant Therapy

At present, monotherapy with oral antioxidant medications has proven to be minimally efficacious in the treatment of acute phase PD, and as such, their use is not supported by the AUA guidelines. However, some recent literature suggests the possible efficacy of oral antioxidants in combination with other non-surgical treatment modalities. Of note, these combination therapies have been utilized in patients with acute and stable phase PD. The role of oxidative stress in the pathophysiology of PD has previously been described in this review and helps elucidate how antioxidant therapy could potentially aid in the treatment of PD.

Paulis et al reported better efficacy of multiple antioxidants over a single agent in 120 active phase PD patients.[96] Patients were assigned in a non-randomized fashion to one of five distinct groups corresponding to a single oral antioxidant, two oral antioxidants, three oral antioxidants, five oral antioxidants and topical diclofenac, and five oral antioxidants with topical diclofenac, and pentoxifylline by perilesional injection. The oral antioxidants used were silymarin, propolis, bilberry, vitamin E, ginkgo biloba. The treatment protocol involved six months of daily oral and topical therapy, along with twice monthly injections in the case of the final group. Combination therapies utilizing the most antioxidants resulted in a corresponding increased improvement in penile pain, plaque volume, curvature, and IIEF scores. Notably, while very limited statistically significant differences in outcome parameters were noted between contiguous groups, a multitude of statistically significant differences in parameters such as plaque volume, penile curvature, and symptom scores were noted between the group with topical diclofenac and the group receiving perilesional injections of pentoxifylline. While this does add credence to the hypothesis that additional antioxidant therapies do improve outcomes, it should be noted that no description on injection technique is provided by the authors. It could be that the act of introducing trauma from the injection needle could be eliciting changes in plaque microarchitecture, as noted in the placebo arm of the IMPRESS trials.[48] Of note, in the IMPRESS trials, patients received injections directly into the plaque and the authors of this study specify perilesional injections. However, without a placebo-controlled arm, one must account for this possibility.

More recently, Paulis et al published a case report of three cases that showed full plaque regression, curvature improvement, and resolution of pain with a combination of oral antioxidants and topical propolis crème in one case and with the addition of pentoxifylline injections in the other two cases.[97] The authors do not specify what phase of disease these patients were in but do report that full regression required between two and four years of therapy. Penile ultrasound was utilized to monitor plaque regression. The oral antioxidants used were silymarin, Ginkgo biloba, propolis, bilberry, and vitamin E. The regiment consisted of daily oral antioxidants, twice daily propolis crème application, and injections every 15 days for six months during initial treatment cycles. During subsequent treatment cycles, injections were spaced out to monthly and every other month. In this limited case-series, the authors do highlight that an experienced provider conducted all the treatments and monitored the plaques. Thus, while positive results were achieved, the external validity of the study must be considered as these patients were treated by a single, high volume PD provider. In addition, given no placebo arm, it must be once again noted that injection trauma alone could play a role in plaque changes, irrespective of the use of antioxidants.

It should be noted that while combination antioxidant therapy is a novel treatment modality that has shown some early positive results, the data is still very limited, especially considering the lack of placebo-controlled trials. Much more research is necessary to validate whether antioxidant usage plays a role in altering PD microarchitecture or if the changes seen in these studies are a result of confounding factors such as needle trauma.

Conclusion

The treatment of PD is constantly evolving. A review of the currently available outcomes literature illustrates a need for more RCTs that utilize similar treatment protocols, patient populations, and standardized outcomes measures. The data from these trials will help to optimize treatment efficacy and delineate what patient factors may contribute to improved outcomes for each treatment modality. Additionally, more data on the long-term effects of these treatments will be important to understand treatment durability and any delayed adverse outcomes. Furthermore, as new treatment modalities arise, they must be evaluated with these same standards before widespread adoption can be undertaken. By

taking these steps, the urologic community will ensure that each PD patient is receiving a safe and effective treatment plan that is tailored to their clinical profile and ensure continued high-quality research into factors that could further improve outcomes in this population.

Disclosure

Dr Larry I Lipshultz is consultant for AbbVie, Aytu BioScience, Clarus Therapeutics, Contraline, Inc., Lipocine, and Endo Pharmaceuticals; advisor for Inherent Biosciences, speaker for American Medical Systems/Boston Scientific; and stockholder of Augmenta LLC, outside the submitted work. The authors report no other conflicts of interest in this work.

References

1. Carriere SP, Pytell JD, Saltzman AF, Fuselier HA. Peyronie's Disease: a Historical Perspective. *Am J Mens Health*. 2014;8(5):434–439. doi:10.1177/1557988314520951
2. Al-Thakafi S, Al-Hathal N. Peyronie's disease: a literature review on epidemiology, genetics, pathophysiology, diagnosis and work-up. *Transl Androl Urol*. 2016;5(3):280–289. doi:10.21037/tau.2016.04.05
3. Loftus CJ, Rajanahally S, Holt SK, Raheem OA, Ostrowski KA, Walsh TJ. Treatment trends and cost associated with Peyronie's disease. *Sex Med*. 2020;8(4):673–678. doi:10.1016/j.esxm.2020.08.003
4. Miner MM, Seftel AD. Peyronie's disease: epidemiology, diagnosis, and management. *Curr Med Res Opin*. 2014;30(1):113–120. doi:10.1185/03007995.2013.842544
5. Mulhall JP, Schiff J, Guhring P. An analysis of the natural history of Peyronie's disease. *J Urol*. 2006;175(6):2115–8; discussion 2118. doi:10.1016/s0022-5347(06)00270-9
6. Di Maida F, Cito G, Lambertini L, et al. The natural history of Peyronie's disease. *World J Mens Health*. 2021;39(3):399–405. doi:10.5534/wjmh.200065
7. De Rose AF, Mantica G, Bocca B, Szpytko A, Van der Merwe A, Terrone C. Supporting the role of penile trauma and micro-trauma in the etiology of Peyronie's disease. Prospective observational study using the electronic microscope to examine two types of plaques. *Aging Male*. 2020;23(5):740–745. doi:10.1080/13685538.2019.1586870
8. Casabé A, Bechara A, Cheliz G, De Bonis W, Rey H. Risk factors of Peyronie's disease. What does our clinical experience show? *J Sex Med*. 2011;8(2):518–523. doi:10.1111/j.1743-6109.2010.02072.x
9. Bjekic MD, Vlajinac HD, Sipetic SB, Marinkovic JM. Risk factors for Peyronie's disease: a case-control study. *BJU Int*. 2006;97(3):570–574. doi:10.1111/j.1464-410X.2006.05969.x
10. Demling RH. The role of anabolic hormones for wound healing in catabolic states. *J Burns Wounds*. 2005;4:e2.
11. Can O, Özbir S, Atalay HA, Çakır SS, Culha MG, Canat HL. The relationship between testosterone levels and Peyronie's disease. *Andrologia*. 2020;52(9):e13727. doi:10.1111/and.13727
12. Lue TF. Peyronie's disease: an anatomically-based hypothesis and beyond. *Int J Impot Res*. 2002;14(5):411–413. doi:10.1038/sj.ijir.3900876
13. El-Sakka AI, Salabas E, Dinçer M, Kadioglu A. The pathophysiology of Peyronie's disease. *Arab J Urol*. 2013;11(3):272–277. doi:10.1016/j.aju.2013.06.006
14. Davila HH, Ferrini MG, Rajfer J, Gonzalez-Cadavid NF. Fibrin as an inducer of fibrosis in the tunica albuginea of the rat: a new animal model of Peyronie's disease. *BJU Int*. 2003;91(9):830–838. doi:10.1046/j.1464-410x.2003.04224.x
15. Sikka SC, Hellstrom WJ. Role of oxidative stress and antioxidants in Peyronie's disease. *Int J Impot Res*. 2002;14(5):353–360. doi:10.1038/sj.ijir.3900880
16. Watanabe MS, Theodoro TR, Coelho NL, et al. Extracellular matrix alterations in the Peyronie's disease. *J Adv Res*. 2017;8(4):455–461. doi:10.1016/j.jare.2017.06.004
17. Del Carlo M, Cole AA, Levine LA. Differential calcium independent regulation of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases by Interleukin-1β and transforming growth Factor-β in Peyronie's plaque fibroblasts. *J Urol*. 2008;179(6):2447–2455. doi:10.1016/j.juro.2008.01.093
18. Paulis G, Romano G, Paulis L, Barletta D. Recent pathophysiological aspects of Peyronie's disease: role of free radicals, rationale, and therapeutic implications for antioxidant Treatment—Literature Review. *Adv Urol*. 2017;2017:4653512. doi:10.1155/2017/4653512
19. Zhang F, Qin F, Yuan J. Molecular mechanisms and current pharmacotherapy of Peyronie's disease: a review. *Front Pharmacol*. 2021;12:643641. doi:10.3389/fphar.2021.643641
20. Chung E, De Young L, Solomon M, Brock GB. Peyronie's disease and mechanotransduction: an in vitro analysis of the cellular changes to Peyronie's disease in a cell-culture strain system. *J Sex Med*. 2013;10(5):1259–1267. doi:10.1111/jsm.12082
21. Hatfield BS, King CR, Udager AM, et al. Peyronie disease: a clinicopathologic study of 71 cases with emphasis on histopathologic patterns and prevalent metaplastic ossification. *Hum Pathol*. 2020;104:9–17. doi:10.1016/j.humpath.2020.07.013
22. Patel DP, Christensen MB, Hotaling JM, Pastuszak AW. A review of inflammation and fibrosis: implications for the pathogenesis of Peyronie's disease. *World J Urol*. 2020;38(2):253–261. doi:10.1007/s00345-019-02815-6
23. Castiglione F, Hedlund P, Weyne E, et al. Intratunical injection of human adipose tissue–derived stem cells restores collagen III/I ratio in a rat model of chronic Peyronie's disease. *Sex Med*. 2019;7(1):94–103. doi:10.1016/j.esxm.2018.09.003
24. Ustriyana P, Hennefarth MR, Srirangapatanam S, et al. Mineralized Peyronie's plaque has a phenotypic resemblance to bone. *Acta Biomater*. 2022;140:457–466. doi:10.1016/j.actbio.2021.11.025
25. Gonzalez-Cadavid NF, Magee TR, Ferrini M, Qian A, Vernet D, Rajfer J. Gene expression in Peyronie's disease. *Int J Impot Res*. 2002;14(5):361–374. doi:10.1038/sj.ijir.3900873
26. Rainer QC, Rodriguez AA, Bajic P, Galor A, Ramasamy R, Masterson TA. Implications of calcification in Peyronie's disease, a review of the literature. *Urology*. 2021;152:52–59. doi:10.1016/j.urology.2021.01.007
27. Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's disease: AUA guideline. *J Urol*. 2015;194(3):745–753. doi:10.1016/j.juro.2015.05.098

28. Bilgutay AN, Pastuszak AW. Peyronie's disease: a review of etiology, diagnosis, and management. *Curr Sex Health Rep*. 2015;7(2):117–131. doi:10.1007/s11930-015-0045-y
29. Alwaal A, Awad M, Boggs N, Kuzbel J, Snoad B. Sexual health inventory for men questionnaire as a screening method for erectile dysfunction in a general urology clinic. *Sex Med*. 2020;8(4):660–663. doi:10.1016/j.esxm.2020.08.002
30. Bacal V, Rumohr J, Sturm R, Lipshultz LI, Schumacher M, Grober ED. Correlation of degree of penile curvature between patient estimates and objective measures among men with Peyronie's disease. *J Sex Med*. 2009;6(3):862–865. doi:10.1111/j.1743-6109.2008.01158.x
31. Wang CX, Flick TR, Patel AH, Sanchez F, Sherman WF. Patients with Dupuytren's contracture, Ledderhose disease, and Peyronie's Disease are at higher risk of arthrofibrosis following total knee arthroplasty. *Knee*. 2021;29:190–200. doi:10.1016/j.knee.2021.02.009
32. Chen JY, Hockenberry MS, Lipshultz LI. Objective assessments of Peyronie's disease. *Sex Med Rev*. 2018;6(3):438–445. doi:10.1016/j.sxmr.2017.12.006
33. Pawłowska E, Bianek-Bodzak A. Imaging modalities and clinical assesment in men affected with Peyronie's disease. *Pol J Radiol*. 2011;76(3):33–37.
34. Hoyland K, Vasdev N, Adshead J. The use of vacuum erection devices in erectile dysfunction after radical prostatectomy. *Rev Urol*. 2013;15(2):67–71.
35. Lin H, Wang R. The science of vacuum erectile device in penile rehabilitation after radical prostatectomy. *Transl Androl Urol*. 2013;2(1):61–66. doi:10.3978/j.issn.2223-4683.2013.01.04
36. Levine LA, Newell M, Taylor FL. Penile traction therapy for treatment of Peyronie's disease: a single-center pilot study. *J Sex Med*. 2008;5(6):1468–1473. doi:10.1111/j.1743-6109.2008.00814.x
37. Ziegelmann MJ, Farrell MR, Levine LA. Modern treatment strategies for penile prosthetics in Peyronie's disease: a contemporary clinical review. *Asian J Androl*. 2020;22(1):51–59. doi:10.4103/aja.aja_81_19
38. MacDonald LP, Armstrong ML, Lehmann KJ, Acker MR, Langille GM. Outcome analysis of patients with Peyronie's disease who elect for vacuum erection device therapy. *Can Urol Assoc J*. 2020;14(9):E428–e431. doi:10.5489/cuaj.6205
39. Raheem AA, Garaffa G, Raheem TA, et al. The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. *BJU Int*. 2010;106(8):1178–1180. doi:10.1111/j.1464-410X.2010.09365.x
40. Avant RA, Ziegelmann M, Nehra A, Alom M, Kohler T, Trost L. Penile traction therapy and vacuum erection devices in Peyronie's disease. *Sex Med Rev*. 2019;7(2):338–348. doi:10.1016/j.sxmr.2018.02.005
41. Haney NM, Kohn TP, Nichols PE, Jg Hellstrom W. The effect of adjunct mechanical traction on penile length in men undergoing primary treatment for Peyronie's disease: a systematic review and meta-analysis. *Urology*. 2018;122:110–115. doi:10.1016/j.urology.2018.07.039
42. Moncada I, Krishnappa P, Romero J, et al. Penile traction therapy with the new device 'Penimaster PRO' is effective and safe in the stable phase of Peyronie's disease: a controlled multicentre study. *BJU Int*. 2019;123(4):694–702. doi:10.1111/bju.14602
43. Ziegelmann M, Savage J, Toussi A, et al. Outcomes of a novel penile traction device in men with Peyronie's disease: a randomized, single-blind, controlled trial. *J Urol*. 2019;202(3):599–610. doi:10.1097/ju.0000000000000245
44. Capoccia E, Ziegelmann M, Emmerson J, Lankford J, Ofori-Marfoh C, Levine L. Long-term patient-reported outcomes in men with Peyronie's disease undergoing nonsurgical and nonintralesional injection management. *Int J Impot Res*. 2021;33(1):75–81. doi:10.1038/s41443-020-0231-y
45. Bole R, White L, Parikh N, Helo S, Kohler T, Ziegelmann M. A modern review of penile traction monotherapy and combination therapy for the treatment of peyronie's disease. *Int J Impot Res*. 2021;33(3):251–258. doi:10.1038/s41443-020-0247-3
46. Yang KK, Bennett N. The history of collagenase clostridium histolyticum. *Sex Med Rev*. 2015;3(4):289–297. doi:10.1002/smrj.54
47. Peak TC, Mitchell GC, Yafi FA, Hellstrom WJ. Role of collagenase clostridium histolyticum in Peyronie's disease. *Biologics*. 2015;9:107–116. doi:10.2147/btt.s65619
48. Gelbard M, Goldstein I, Hellstrom WJ, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled Phase 3 studies. *J Urol*. 2013;190(1):199–207. doi:10.1016/j.juro.2013.01.087
49. Goldstein I, Lipshultz LI, McLane M, et al. Long-term safety and curvature deformity characterization in patients previously treated with collagenase clostridium histolyticum for Peyronie's disease. *J Urol*. 2020;203(6):1191–1197. doi:10.1097/ju.0000000000000743
50. Hellstrom WJG, Tue Nguyen HM, Alzweri L, et al. Intralesional collagenase clostridium histolyticum causes meaningful improvement in men with Peyronie's disease: results of a multi-institutional analysis. *J Urol*. 2019;201(4):777–782. doi:10.1097/ju.0000000000000032
51. Goldstein I, Knoll LD, Lipshultz LI, Smith T, Kaufman GJ, McMahon CG. Changes in the effects of Peyronie's disease after treatment with collagenase clostridium histolyticum: male patients and their female partners. *Sex Med*. 2017;5(2):e124–e130. doi:10.1016/j.esxm.2017.02.001
52. Ziegelmann MJ, Viers BR, McAlvany KL, Bailey GC, Savage JB, Trost LW. Restoration of penile function and patient satisfaction with intralesional collagenase clostridium histolyticum injection for Peyronie's disease. *J Urol*. 2016;195(4 Pt 1):1051–1056. doi:10.1016/j.juro.2015.10.065
53. Nguyen HMT, DeLay KJ, Diao L, et al. Racial variations in response to intralesional collagenase clostridium histolyticum in men with Peyronie's disease. *Transl Androl Urol*. 2017;6(5):888–893. doi:10.21037/tau.2017.07.26
54. Abdel Raheem A, Capece M, Kalejaiye O, et al. Safety and effectiveness of collagenase clostridium histolyticum in the treatment of Peyronie's disease using a new modified shortened protocol. *BJU Int*. 2017;120(5):717–723. doi:10.1111/bju.13932
55. Cocci A, Russo GI, Briganti A, et al. Predictors of treatment success after collagenase Clostridium histolyticum injection for Peyronie's disease: development of a nomogram from a multicentre single-arm, non-placebo controlled clinical study. *BJU Int*. 2018;122(4):680–687. doi:10.1111/bju.14410
56. Capece M, Cocci A, Russo G, et al. Collagenase clostridium histolyticum for the treatment of Peyronie's disease: a prospective Italian multicentric study. *Andrology*. 2018;6(4):564–567. doi:10.1111/andr.12497
57. Cao D, Li J, Lu Y, et al. Efficacy and safety of collagenase clostridium histolyticum in the treatment of Peyronie's disease: an evidence-based analysis. *Front Med*. 2022;9:780956. doi:10.3389/fmed.2022.780956
58. Carson CC, Sadeghi-Nejad H, Tursi JP, et al. Analysis of the clinical safety of intralesional injection of collagenase Clostridium histolyticum (CCH) for adults with Peyronie's disease (PD). *BJU Int*. 2015;116(5):815–822. doi:10.1111/bju.13120
59. Lipshultz LI, Goldstein I, Seftel AD, et al. Clinical efficacy of collagenase Clostridium histolyticum in the treatment of Peyronie's disease by subgroup: results from two large, double-blind, randomized, placebo-controlled, Phase III studies. *BJU Int*. 2015;116(4):650–656. doi:10.1111/bju.13096

60. Diao L, Anaissie J, Nguyen HMT, et al. Effect of collagenase Clostridium histolyticum on penile vascular and morphological parameters in patients with Peyronie's disease. *Transl Androl Urol*. 2017;6(5):894–898. doi:10.21037/tau.2017.07.27
61. Yafi FA, Hatzichristodoulou G, Knoedler CJ, Trost LW, Sikka SC, Hellstrom WJ. Comparative analysis of tunical plication vs. intralesional injection therapy for ventral Peyronie's disease. *J Sex Med*. 2015;12(12):2492–2498. doi:10.1111/jsm.13072
62. Greenberg J, Soubra A, Kim J, et al. Xiaflex® treatment for Peyronie's disease may improve penile curvature degree with no effect on the loss on penile length in post-marketing analysis. *J Sex Med*. 2022;19(4):S36–S37.
63. Wymer K, Ziegelmann M, Savage J, Kohler T, Trost L. Plaque calcification: an important predictor of collagenase clostridium histolyticum treatment outcomes for men with Peyronie's Disease. *Urology*. 2018;119:109–114. doi:10.1016/j.urology.2018.06.003
64. Bajic P, Wiggins AB, Ziegelmann MJ, Levine LA. Characteristics of men with Peyronie's disease and collagenase clostridium histolyticum treatment failure: predictors of surgical intervention and outcomes. *J Sex Med*. 2020;17(5):1005–1011. doi:10.1016/j.jsxm.2020.02.002
65. Yousif A, Tue Nguyen HM, Shalaby H, Hellstrom W. MP33-17 efficacy and safety of collagenase Clostridium Histolyticum (CCH) treatment in Peyronie's disease patients with and without calcification. *J Urol*. 2020;203(Supplement 4):e501–e501.
66. Heslop D, Helo S, Houlihan M, Bajic P, Kohler T, Ziegelmann M. MP33-09 hourglass deformity portends a lower likelihood of restoring penetration and preventing surgery with collagenase for Peyronie's disease. *J Urol*. 2020;203(Supplement 4):e497–e498.
67. Chung E, Garcia F, Young LD, Solomon M, Brock GB. A comparative study of the efficacy of intralesional verapamil versus normal saline injection in a novel Peyronie disease animal model: assessment of immunohistopathological changes and erectile function outcome. *J Urol*. 2013;189(1):380–384. doi:10.1016/j.juro.2012.08.191
68. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. *J Urol*. 1994;151(6):1522–1524. doi:10.1016/s0022-5347(17)35291-6
69. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol*. 2002;168(2):621–5; discussion 625–6. doi:10.1016/s0022-5347(05)64691-5
70. Favilla V, Russo GI, Zucchi A, et al. Evaluation of intralesional injection of hyaluronic acid compared with verapamil in Peyronie's disease: preliminary results from a prospective, double-blinded, randomized study. *Andrology*. 2017;5(4):771–775. doi:10.1111/andr.12368
71. Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. *Urology*. 1998;51(4):620–626. doi:10.1016/s0090-4295(97)00700-0
72. Shirazi M, Haghpanah AR, Badiee M, Afrasiabi MA, Haghpanah S. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. *Int Urol Nephrol*. 2009;41(3):467–471. doi:10.1007/s11255-009-9522-4
73. Greenfield JM, Shah SJ, Levine LA. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol*. 2007;177(3):972–975. doi:10.1016/j.juro.2006.10.065
74. Duncan MR, Berman B, Nseyo UO. Regulation of the proliferation and biosynthetic activities of cultured human Peyronie's disease fibroblasts by interferons-alpha, -beta and -gamma. *Scand J Urol Nephrol*. 1991;25(2):89–94. doi:10.3109/00365599109024539
75. Hellstrom WJ, Kendirci M, Matern R, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. *J Urol*. 2006;176(1):394–398. doi:10.1016/s0022-5347(06)00517-9
76. Trost LW, Ates E, Powers M, Sikka S, Hellstrom WJ. Outcomes of intralesional interferon-α2B for the treatment of Peyronie disease. *J Urol*. 2013;190(6):2194–2199. doi:10.1016/j.juro.2013.05.022
77. Stewart CA, Yafi FA, Knoedler M, et al. Intralesional injection of interferon-α2b improves penile curvature in men with Peyronie's disease independent of plaque location. *J Urol*. 2015;194(6):1704–1707. doi:10.1016/j.juro.2015.06.096
78. Sokhal AK, Jain NK, Jhanwar A, Singh K, Saini DK. Prospective study to evaluate the clinical outcome of intralesional interferon-α2b in the management of Peyronie's disease. *Urol Ann*. 2018;10(2):154–158. doi:10.4103/ua.ua_65_17
79. Alom M, Meng Y, Nguyen HM, et al. MP33-06 intralesional collagenase clostridium histolyticum achieves greater curvature improvements compared to interferon for Peyronie's disease. *J Urol*. 2020;203(Supplement 4):e496.
80. Inal T, Tokatli Z, Akand M, Ozdiler E, Yaman O. Effect of intralesional interferon-alpha 2b combined with oral vitamin E for treatment of early stage Peyronie's disease: a randomized and prospective study. *Urology*. 2006;67(5):1038–1042. doi:10.1016/j.urology.2005.11.005
81. Sun J, Gao F, Wang Y, Sun W, Jiang B, Li Z. Extracorporeal shock wave therapy is effective in treating chronic plantar fasciitis: a meta-analysis of RCTs. *Medicine*. 2017;96(15):e6621. doi:10.1097/md.0000000000006621
82. Speed C. A systematic review of shockwave therapies in soft tissue conditions: focusing on the evidence. *Br J Sports Med*. 2014;48 (21):1538–1542. doi:10.1136/bjsports-2012-091961
83. Raheem OA, Natale C, Dick B, et al. Novel treatments of erectile dysfunction: review of the current literature. *Sex Med Rev*. 2021;9(1):123–132. doi:10.1016/j.sxmr.2020.03.005
84. Ortac M, Özmez A, Cilesiz NC, Demirelli E, Kadıoğlu A. The impact of extracorporeal shock wave therapy for the treatment of young patients with vasculogenic mild erectile dysfunction: a prospective randomized single-blind, sham controlled study. *Andrology*. 2021;9(5):1571–1578. doi:10.1111/andr.13007
85. Di Mauro M, Russo GI, Della Camera PA, et al. Extracorporeal shock wave therapy in Peyronie's disease: clinical efficacy and safety from a single-arm observational study. *World J Mens Health*. 2019;37(3):339–346. doi:10.5534/wjmh.180100
86. Bakr AM, El-Sakka AI. Extracorporeal shockwave therapy in Peyronie's Disease: systematic review and meta-analysis. *J Sex Med*. 2021;18 (10):1705–1714. doi:10.1016/j.jsxm.2021.06.012
87. Abdessater M, Akakpo W, Kanbar A, et al. Low-intensity extracorporeal shock wave therapy for Peyronie's disease: a single-center experience. *Asian J Androl*. 2022;24(1):45–49. doi:10.4103/aja.aja_40_21
88. Alves R, Grimalt R. A review of platelet-rich plasma: history, biology, mechanism of action, and classification. *Skin Append Disord*. 2018;4 (1):18–24. doi:10.1159/000477353
89. Poulios E, Mykoniatis I, Pyrgidis N, et al. Platelet-Rich Plasma (PRP) improves erectile function: a double-blind, randomized, placebo-controlled clinical trial. *J Sex Med*. 2021;18(5):926–935. doi:10.1016/j.jsxm.2021.03.008
90. Everts P, Onishi K, Jayaram P, Lana JF, Mautner K. Platelet-rich plasma: new performance understandings and therapeutic considerations in 2020. *Int J Mol Sci*. 2020;21(20). doi:10.3390/ijms21207794
91. Notsek M, Boiko M. PO-01-083 Platelet-rich plasma therapy of Peyronie's disease. *J Sex Med*. 2019;16(5):S70.

92. Matz EL, Pearlman AM, Terlecki RP. Safety and feasibility of platelet rich fibrin matrix injections for treatment of common urologic conditions. *Invest Clin Urol*. 2018;59(1):61–65. doi:10.4111/icu.2018.59.1.61
93. Virag R, Sussman H. PS-05-007 Plasma rich platelets and hyaluronic acid improves peyronie's disease: a case control study of 75 cases. *J Sex Med*. 2017;14(4):e121.
94. Khodamoradi K, Dullea A, Golan R, et al. Platelet Rich Plasma (PRP) growth factor concentration varies in men with erectile dysfunction. *J Sex Med*. 2022. doi:10.1016/j.jsxm.2022.06.003
95. Alkandari MH, Touma N, Carrier S. Platelet-rich plasma injections for erectile dysfunction and Peyronie's disease: a systematic review of evidence. *Sex Med Rev*. 2022;10(2):341–352. doi:10.1016/j.sxmr.2020.12.004
96. Paulis G, Paulis A, Romano G, Barletta D, Fabiani A. Rationale of combination therapy with antioxidants in medical management of Peyronie's disease: results of clinical application. *Res Rep Urol*. 2017;9:129–139. doi:10.2147/rru.s141748
97. Paulis G, De Giorgio G. Full regression of Peyronie's disease plaque following combined antioxidant treatment: a three-case report. *Antioxidants*. 2022;9:1661.