



Peyronie's disease: pharmacological treatments and limitations

Eric V. Li, Robert Esterquest, Minh N. Pham, Evan J. Panken, Channa Amarasekera, Aisha Siebert, Petar Bajic & Laurence A. Levine

To cite this article: Eric V. Li, Robert Esterquest, Minh N. Pham, Evan J. Panken, Channa Amarasekera, Aisha Siebert, Petar Bajic & Laurence A. Levine (2021): Peyronie's disease: pharmacological treatments and limitations, Expert Review of Clinical Pharmacology, DOI: [10.1080/17512433.2021.1903873](https://doi.org/10.1080/17512433.2021.1903873)

To link to this article: <https://doi.org/10.1080/17512433.2021.1903873>



Accepted author version posted online: 15 Mar 2021.



Submit your article to this journal [↗](#)



View related articles [↗](#)



View Crossmark data [↗](#)

Publisher: Taylor & Francis & Informa UK Limited, trading as Taylor & Francis Group

Journal: *Expert Review of Clinical Pharmacology*

DOI: 10.1080/17512433.2021.1903873

Peyronie's disease: pharmacological treatments and limitations

Eric V. Li², Robert Esterquest¹, Minh N. Pham², Evan J. Panken², Channa Amarasekera¹, Aisha Siebert², Petar Bajic³, Laurence A. Levine¹

¹Rush University Medical Center, Division of Urology, Chicago, IL, 60612, United States of America; ²Northwestern University, Feinberg School of Medicine, Department of Urology, Chicago, IL 60611, United States of America; ³Cleveland Clinic, Center for Men's Health, Glickman Urological and Kidney Institute, Cleveland, OH, 44195, United States of America

Correspondence

Channa Amarasekera

Rush University Medical Center,

Division of Urology, Chicago, IL, 60612,

United States of America

Email: Channa.amarasekera@northwestern.edu

Abstract

Introduction: Peyronie's disease (PD) is a disorder of the tunica albuginea from disordered and excessive deposition of collagen resulting in a palpable scar, pain, erect penile deformity and erectile dysfunction that significantly impacts patients both physically and emotionally.

Areas Covered: Several treatment options have been described for PD, including shockwave therapy, traction therapy, both oral and intralesional pharmacological options, and surgery. This review seeks to examine the data for different types of non-surgical treatments for PD. We review how various treatment modalities impact several relevant clinical endpoints for Peyronie's disease, including effects on pain, penile curvature, plaque formation, and erectile function. We performed a literature search using PubMed and SCOPUS while referencing AUA, EAU, and CUA guidelines for management of Peyronie's Disease for studies published 1980-2020.

Expert opinion: Intralesional collagenase injections have the strongest evidence and are the only FDA approved intralesional treatment for PD. Penile traction therapy (PTT) is low risk and may be beneficial in patients willing to invest significant time using the devices. Furthermore, oral combination therapy with other modalities may provide some benefit. Further investigation is required to better understand pathophysiology of PD and clarify the therapeutic utility of existing treatments, potentially with a multimodal strategy.

Keywords: Peyronie's disease, medical management, oral, intralesional, traction, topical

Article highlights

- Intralesional collagenase has the strongest evidence for treatment of PD among intralesional treatments and is the only intralesional treatment approved by the FDA. Intralesional verapamil and interferon α -2b remain off label treatments for PD with weaker evidence.
- The evidence on extracorporeal shockwave therapy (ESWT) in the treatment of PD is conflicting. There is no evidence that ESWT reduces erect penile deformity. ESWT is currently recommended only for the treatment of penile pain in PD patients.
- PTT is suggested to improve penile length, decrease curvature, and increase penile girth when worn daily for 3-4 months, although larger cohorts in well-designed randomized control trials are required to further characterize benefits of traction therapy. While traditional traction devices required patients to wear the device daily for more than 3 hours, the newer Restorex® device has shown improvement with shorter periods of daily use.
- Topical therapies are not currently recommended for treatment of PD by the AUA. The EAU currently only recommends topical verapamil.
- The AUA and EAU do not currently recommend oral therapy for treatment of PD for disease modifying intent due to lack of evidence demonstrating benefit of monotherapy. The agents are prescribed due to the potential benefit in the absence of risks.
- Future research should extend our insights behind the mechanisms leading to PD and uncover the therapeutic value of already existing treatment options. Well-designed, placebo-controlled randomized clinical trials are necessary to refine our current understanding of non-surgical treatments.

1. Introduction

1.1 Definitions and History

Peyronie's disease (PD) is an acquired structural abnormality of the penis due to fibrosis of the tunica albuginea from disordered and excessive deposition of collagen, which may lead to pain, penile deformity, erectile dysfunction and profound emotional distress [1]. PD was described as "induratio penis plastica" in the 18th century by Francois Gigot de la Peyronie of France, after whom the disease is named [2]. However, there are descriptions of the disease many centuries prior, as far back as the 13th century by Theodoricus Borgognoni and Guilielmus Saliceto [3]. Current estimates of the incidence of PD range from 0.5%-20.3%, and it remains an underdiagnosed condition [4, 5]. The 2 phases of PD are the acute phase and the chronic phase. In the acute phase, which may last up to 12 months, the patient may have penile pain, palpable plaques, and worsening penile curvature. In the chronic phase, the penile curvature is stable for >3 months and penile pain generally subsides. Currently, the AUA only recommends surgical intervention in the chronic phase, and generally the acute phase is managed conservatively with many of the treatments discussed in this review (1).

1.2 Pathophysiology of PD

PD is likely caused by either one episode of acute trauma or repeated trauma to the tunica albuginea followed by impaired tissue healing leading to scar formation through deposition of collagen and decreases in elastin [6]. The tunica albuginea is an organized structure involving inner circular and outer longitudinal layers of connective tissue, and Peyronie's Disease is often associated with disruption and disorganization of these connective tissue layers [7]. Therefore, PD is classically associated with various causes of penile trauma, including sexual intercourse, history of penile surgery, or prostatectomy which cause either microscopic or macroscopic trauma to the tunica albuginea. Repetitive trauma to the tunica albuginea in the setting of impaired tissue response to healing leads to increased pro-fibrotic factors such as transforming growth factor- beta (TGF- β) and platelet derived growth factor (PDGF), while decreasing anti-fibrotic factors. Eventually, fibrin develops a meshwork of fibers attracting inflammatory cells and fibroblasts to form scar tissue which is further exacerbated for formation of reactive oxygen species [8]. Other disease states with impaired healing response, such as Dupuytren's contracture

and Paget's disease of the bone are associated with PD, as is a family history of PD. Furthermore, *in vitro* studies suggest that failure of the plaque tissue to remodel properly may be due to excess TIMPs (tissue inhibitors of metalloproteinases), which results in a persistent scar [9]. Furthermore, cardiovascular diseases such as diabetes mellitus, hypertension, hyperlipidemia, heart disease, and smoking decrease perfusion to the penis and can also negatively impact penile healing. This disordered healing leads to scar/plaque formation which ultimately results in penile curvature. The pathophysiology of PD is complex and multifactorial but is thought to arise from repeated traumatic insult followed by dysregulated healing response in the setting of genetic predisposition and cardiovascular comorbidities (Figure 1).

1.3 Aims

Several treatment options have been described with various mechanisms of action, including non-medical therapies (traction and shock wave therapy), medical therapies (oral pharmacotherapy, topical therapy and intralesional injections), and surgical interventions. The goals of treatment typically include modifying the penile curvature and deformity to allow for penetrative intercourse.

Our aim is to review studies evaluating the different types of non-surgical treatments for Peyronie's disease. We focus on the impact each treatment modality on success as it relates to the correction of curvature or deformity, its impact on pain, and erectile function, when such data are available.

2. Intralesional therapies

2.1 Intralesional Verapamil

Verapamil was first proposed to have benefit in *in vitro* studies, which demonstrated that formation of extracellular matrices with collagen and glycosaminoglycans ultimately resulting in plaque formation is a calcium dependent pathway [10]. Calcium modifies cytokine release as well as several growth factors instrumental in formation of fibrosis. Verapamil is a versatile calcium channel blocker use, and in this context modifies the fibrosis that occurs in PD. Levine and colleagues first demonstrated significant clinical improvement in a cohort of 14 patients with

Peyronie's disease in 1994, reporting a reduction of plaque volume >50% in 30% of patients, and stable or improved plaque related changes in 83% of patients [11]. Levine and colleagues then published a prospective non-randomized cohort of 156 men, reporting that 84% of men had resolution of pain (typically within 2-3 injections), and 60% of men had objective improvement penile curvature with a mean improvement of 31°. Subjective rigidity was improved in 80% of patients and sexual performance was improved in 71% [12]. However, several subsequent studies have failed to demonstrate significant improvement with intralesional verapamil [13, 14]. For example, Bennett and colleagues reported 60% patients had unchanged penile curvature, although this cohort had 100% resolution of penile pain [15]. Intralesional verapamil appears to have the most rapid reported resolution of pain, with 97% of patients seeing resolution of pain after a mean of 2.5 injections (Table 1 for summary of intralesional therapy trials) [16].

Verapamil may be efficacious when combined with oral Vitamin E, with statistically significant improvements in penile pain and improvement of sexual function when comparing intralesional verapamil plus vitamin E versus intralesional verapamil alone [17]. The most common adverse events are penile bruising, headaches, sweating, loss of libido, and injection site pain. The dosage is 10 mg (diluted in 2 mL injectable saline) every other week for 3-6 months. Given the weak and conflicting evidence for verapamil, intralesional verapamil currently has a conditional recommendation in AUA guidelines for the management of Peyronie's disease [1].

2.2 Interferon α -2b

Interferon α -2b was initially described *in vitro* to decrease fibroblast and extracellular collagen production while increasing collagenase production [18]. Wegner and colleagues first studied use of intralesional interferon α -2b for Peyronie's disease, reporting that 19/25 (76%) patients had stable or decreasing plaque size [19]. In 2005, Kendirci and colleagues reported significant decreases in penile curvature (mean absolute improvement 12°, 48.8° pre-treatment vs. 36.8° post-treatment), plaque size, and pain with erections in an unblinded prospective randomized controlled trial with 39 patients. This trial also reported improvement in peak systolic pressure and calculated resistive indices on duplex ultrasound compared to controls [20]. Hellstrom and colleagues, and Trost and colleagues reported similar modest improvements in penile curvature (mean absolute improvement 13.5° and 9°, respectively), plaque size/density, and pain as well as

improved penile flow parameters in larger cohorts [21, 22]. All trials reported mild side effects such as sinusitis, flu-like symptoms (fevers, chills, arthralgias), and minor penile ecchymosis, which were self-limited within 48 hours of treatment and managed with non-steroidal anti-inflammatory drugs (NSAIDs). It is typically administered $1-5 \times 10^6$ units weekly or biweekly for 1-6 months. Furthermore, Stewart and colleagues found that intralesional interferon treatment was efficacious for both dorsal and ventral plaques, with >20% decrease in penile curvature in 54% and 52% of patients, respectively ($p=0.92$) [23]. Despite the data suggesting its efficacy, interferon comes with a significant financial cost and remains an off-label treatment for Peyronie's disease, providing modest improvements in degree of penile curvature with a moderate recommendation [1].

2.3 Collagenase Clostridium Histolyticum

Collagenase Clostridium Histolyticum is an enzyme produced by Clostridium histolyticum naturally which actively degrades the collagen found in plaques. Gelbard and colleagues initially reported that Collagenase Clostridium Histolyticum (CCH) was effective in degradation of penile plaques and improvement of penile curvature both *in vivo* and *in vitro* in the 1980s [24, 25]. The first major clinical trials for treatment of Peyronie's disease, the Investigation for Maximal Peyronie's Efficacy and Safety Studies (IMPRESS) I and II, have advanced the medical management of Peyronie's disease with the only currently FDA-approved intralesional treatment. A combined post-hoc analysis by Gelbard and colleagues in 2013 showed a mean improvement in penile curvature by 7.7° compared to placebo and a 1-point improvement in Peyronie's disease symptom bother score (-2.8 vs. -1.8) compared to placebo [26]. The protocol used in these trials were up to 4 cycles of 2 injections spaced 1-3 days apart followed by in person penile modeling with injection of 0.58 mg CCH in 0.25 mL saline solution every 6 weeks. Lipshultz and colleagues performed subgroup analyses based on severity of penile curvature at baseline ($30-60^\circ$ vs $61-90^\circ$), Peyronie's disease duration, degree of plaque calcification, and baseline erectile function, finding significant improvements in penile curvature and symptom bother reductions in all subgroups [27]. Another multi-institutional retrospective cohort in 2019 of 918 men demonstrated 33% improvement in penile curvature (49.7° pre-treatment to 32.7° after treatment), with 74.4% men experiencing 20% or greater improvement in curvature, and an association between the number of cycles of CCH and curvature improvement

[28]. Notably, patients with curvature $<30^\circ$ or $>90^\circ$, isolated hourglass deformities, calcified plaques, or plaques causing curvature proximal to penile base were excluded from the original trials, and results may not be generalizable to these subgroups. Penile ecchymosis, swelling, and pain were the most common reported side effects. In the combined IMPRESS trials, 6/551 (1.1%) men experienced serious AEs, three corporeal ruptures repaired surgically and well as three penile hematomas, one of which required surgical exploration. Furthermore, 17% of the men in Hellstrom et al's multi-institutional study were in the acute phase of PD and there was no statistically significant difference between the acute and stable phase. Nguyen et al also compared 36 patients in the acute phase and 126 patients in the stable phase and also found no statistically significant difference in improvements with PD, suggesting that CCH is efficacious in both phases of PD [29]. As a result of the multiple trials demonstrating efficacy of CCH, the AUA currently gives a moderate recommendation for use of CCH to reduce penile curvature of $30\text{-}90^\circ$ in the setting of stable Peyronie's disease and intact erectile function and can be efficacious in both the acute and stable phase of PD [1].

3. Extracorporeal Shockwave Therapy (ESWT)

Extracorporeal shockwave therapy (ESWT) is a non-invasive treatment modality that currently has a conditional recommendation for treatment of penile pain but is not currently indicated for reduction of penile curvature or plaque size for PD. Shockwave therapy is used in a variety of contexts such as muscular disorders, peripheral vascular disease, and wound healing, and is hypothesized to be a non-invasive physical form of regenerative medicine. Mechanical therapy regulates several cell signal pathways such as Wnt, vascular endothelial growth factor (VEGF), and brain-derived neurotrophic factor (BDNF) which all ultimately modulate tissue regeneration and stem cell proliferation [30]. Shockwave therapy has become one of the gold standard treatments for the management of renal calculi and is utilized in the treatment of a number of musculoskeletal conditions for its anti-inflammatory properties [31, 32]. It is hypothesized that ESWT treats PD by two different mechanisms. ESWT applies direct force on the plaque, leading to mechanical induced remodeling and plaque lysis, and also promotes angiogenesis, leading to increased availability of inflammatory mediators causing plaque lysis and absorption [30, 33].

The use of ESWT for the treatment of PD was first discussed in the literature in 1989 [34]. In 1999, Abdel-Salam and colleagues treated 24 men with ESWT who had failed prior non-surgical management for PD. In this non-controlled study, ten patients (42%) reported resolution of painful erections with improvement of the penile angulation after therapy, while four patients (17%) reported complete remission of signs and symptoms [35].

The first randomized, double-blind, placebo-controlled clinical trial for the application of ESWT in Peyronie's disease was published by Palmieri and colleagues in 2009 in a cohort of 100 PD patients who had not been previously treated for PD [36]. The trial reported significantly improved quality of life and erectile function as measured by the visual analog scale (VAS), International Index of Erectile Function (IIEF-5), and QoL score. Although there were no significant differences in plaque size or penile curvature after 24 weeks in the ESWT group, the placebo group experienced significant worsening of both parameters, suggesting that ESWT may have a role in preventing disease progression [36]. Other studies have shown an improvement in penile pain, but report varying results on plaque size, penile curvature, and erectile function. For example, one subsequent study by Chitale and colleagues randomized 36 men to six sessions of ESWT or sham treatment, reporting no significant differences in plaque size, penile angulation, or erectile function in patients treated with short-term ESWT [37]. In 2013, Hatzichristodoulou and colleagues randomized 102 men to ESWT or placebo for 6 weeks and found a statistically significant decrease in pain between the two groups, 85% in the ESWT group compared to 48% in the placebo group, with no significant differences in plaque size [38]. Furthermore, penile deviation progressed in 40% of the ESWT group compared to 24.5% of the placebo group [38]. A 2016 meta-analysis including six studies with 443 men found a significant decrease in plaque size and improvement in pain, with no significant difference in improvement of penile curvature and sexual function [39]. This is in line with contemporary studies showing no correlation between plaque size and degree of curvature when looking at the PD population in general [40].

Given the conflicting evidence of improvement in penile curvature and sexual function, ESWT is currently only recommended to treat pain associated with PD in the AUA, EAU, and Canadian Urological Association (CUA) [1, 33, 41]. The current studies have variable inclusion criteria, differences in ESWT protocol, small sample sizes, and in many, a lack of controls, necessitating further high quality, randomized controlled trials to further investigate the role of

ESWT in PD. Furthermore, the utility of ESWT for pain management has been questioned as the majority of patients (89%) with PD experience resolution of pain by 12 months without intervention [42]. In conclusion, the data on ESWT in the treatment of PD remains unclear and is only currently recommended for treatment of penile pain.

4. Traction Therapy

Penile Traction Therapy (PTT) is a relatively new treatment that was first described in 2001 [43]. Traction therapies use direct force application to the penis and result in remodeling of the extracellular matrix of the plaque via mechanically induced signal transduction pathways and gene regulatory mechanisms. Animal models studying traction devices in correction of penile curvature hypothesize that mechanical therapy may counter fibrosis, cell apoptosis, and smooth muscle death [44]. These devices vary in size and shape but tend to follow a similar principle of using parallel rods connecting 2 padding rings, one at the base of the penis in the suprapubic area and the second at the corona of the penis. Recently, new devices have been produced, which differ from this traditional model. For example, RestoreX® uses a ratcheting body with springs and generates longitudinal and oppositional angular forces that generate up to 7lbs of force at specific plaque formation sites. It utilizes a penile clamp at the corona to distribute force throughout the penis to avoid potential skin irritation associated with traditional devices. Alternatively, the PeniMasterPro® uses a non-compressing suction cup apparatus over the glans with an elastic belt, or rod system, which can be worn during the day to generate traction. Penile traction has been studied both as a primary treatment as well as adjunct treatment in addition to intralesional injections and surgery. However, many studies are limited by their study design as the nature of the disease and associated psychological stress generally result in cohort studies with small sample sizes without a control arm.

Scroppo and colleagues first characterized an improvement in penile curvature with traction therapy in 8 men with PD [43]. Men with a minimum of 3 months of PD without concomitant erectile dysfunction (ED) were included in the study and instructed to use the traction device for at least 4 hours a day for 3–6 months. The authors reported non-significant increase in mean penile length (4.1 mm, 100.5 mm before PTT vs. 104.6 mm after PTT) ($p > 0.05$), and a

significant decrease in mean penile curvature of 14° (34° before PTT vs 20° after PTT) ($p < 0.05$).

In 2008, Levine and colleagues published on a non-controlled pilot study of 10 men using the FastSize Penile Extender for 2-8 hours/day for 6 months, characterizing changes in penile curvature, penile girth, and parameters on dynamic duplex ultrasound [45]. This study reported reduced curvature in all men, (range 10°- 45°, median decrease in curvature 33%), increased penile length (range 0.5-2 cm), and increase in girth (range 0.5-1 cm). 4/4 men with reported hinge effects due to indentation or hourglass deformity at the study's initiation noted improvement or complete resolution with enhanced axial rigidity. PTT was well tolerated, with no changes in penile sensation, new onset erectile dysfunction, or skin injury.

In 2014, Martinez-Salamanca and colleagues demonstrated increases in penile length, decreases in penile curvature, and improvements in sonographically detectable penile plaques in a cohort of 55 patients in the acute phase of PD who received 6 months of traction therapy compared to 41 patients with PD who did not receive active treatment [46]. The acute phase was defined as a clinical diagnosis of PD within the last 12 months. After treatment, PTT users were significantly more likely to experience increases in stretch penile length (1.5 vs. -2.6 cm) and decrease in mean penile curvature (-18° vs 23°). The percentage of patients who were not able to achieve penetration significantly decreased from 62% to 20% ($P < 0.03$). Furthermore, PTT was associated with resolution of sonographic penile plaques in 48% of patients with PD and decreased the need for surgery by 40% in patients who were initially good candidates for surgery. This highlights traction therapy as an effective option in the acute phase, particularly as the acute phase is most commonly associated with penile pain.

Recently, Moncada and colleagues studied the new Penimaster ® PRO in a cohort of 93 patients with chronic stable PD [47]. 47 were randomly assigned to the Penimaster ® PRO group (PG) and 46 to the non-intervention group (control). Patients applied the traction device for 3-8 hours a day for 12 consecutive weeks. The PG group had significant mean absolute reductions in penile curvature of 31.2° ($P < 0.001$), with mean 41.1% improvement from baseline. Furthermore, the study noted a dose-dependent response, as patients who used PTT <4h/day had absolute

reductions of 15°-25° in penile curvature, while patients using the device >6h/day ranged from 20°-50° in absolute penile curvature reduction.

Ziegelmann and colleagues studied 110 men in a randomized control trial comparing the RestoreX® penile traction device to no therapy (control) [48]. Groups of 38 men were assigned to one of 4 arms of the study: no therapy (control) or with treatment of with RestoreX® for 30 minutes sessions for either 1, 2, or 3 times daily for 3 months. Inclusion criteria were no current or previous PD treatments and a $\geq 30^\circ$ curvature. The study authors reported significant improvement in penile length (mean improvement 1.5 cm, $p < 0.001$), curvature (-11.7° vs. 1.3° , $p < 0.01$), and erectile function. Of the men, 25% had a composite response that was 20% or greater curvature improvement with a 1- point or more improvement in the PDQ bother score or a return to penetrative intercourse. No significant adverse events were reported in any group, and no significant differences were noted between traction groupings (1, 2, or 3 times daily).

Previous reviews of traction therapy as single treatment and as conjunction treatment have concluded PTT to be a good and cost-effective treatment for PD [49]. The key to successful PTT is duration, with at least 3 h per day for 3–4 months giving the best chance for a meaningful response [50]. Further randomized control trials with larger cohorts of men are needed to further demonstrate the benefit of PTT in treatment of both active and stable PD.

5. Topical Therapy

Topical therapies are highly desirable as therapeutics due to the low risk of systemic complications, ease of use, and cost-effectiveness. However, there are concerns about tissue concentration within the plaque. To address the question of adequate pharmacologic penetration of topical verapamil, Martin and colleagues evaluated the concentration of verapamil in a section of diseased tunica albuginea by applying a verapamil gel to the affected lesion the night before surgical correction. During surgery, patient's tunica was excised and tested for verapamil levels, and no patients were found to have detectable drug within the tissue sample [50]. Other studies argue that topical drug therapy may take up to 90 days to reach effective concentrations and that the formulation of the drug can affect drug absorption [51].

5.1 *Topical Verapamil*

Verapamil works within the PD plaque by decreasing the incorporation of proline into the extracellular matrix, decreasing the amount of collagen produced by fibroblasts, and increasing collagenase activity [52]. One industry-sponsored placebo-controlled pilot study by Fitch and colleagues, assessed the effectiveness of verapamil hydrochloride 15% gel, a trifluoperazine topical, and magnesium sulfate topical, and no treatment (control), each incorporated in a transdermal vehicle [53]. Patients were randomized into one of 4 arms and treated for 3 months. 15% verapamil gel twice daily for 3 months led to a self-reported 43% mean reduction in curvature compared to 18% in the placebo group. After 3 months, all patients were treated with topical verapamil for 6 additional months. 94.4% of patients reported improvement in their curvature after 9 months. In addition to results being self-reported, limitations include small sample sizes in each arm of the trial ($n = 18$), disease duration heterogeneity (2-15 months, mean 3 years), and curvature severity ($5^{\circ} - 120^{\circ}$, mean 45°). However, this study has been heavily criticized for lack of objective measurements and for lack of a true control group [54]. To date no studies have shown that topical application of verapamil can lead to adequate tissue penetration and topical verapamil is not recommended in the treatment of PD.

5.2 *Transdermal Electromotive Drug Administration (EMDA)*

Concerns about the ability of topical verapamil preparations to penetrate the tunica albuginea led to the exploration of transdermal electromotive drug administration (EDMA). EMDA utilizes an electrical field and electrical current to help drug delivery through the superficial tissues and into the tunica albuginea. One of the first studies evaluating the use of EMDA in the treatment of Peyronie's disease was a non-controlled study done by Montorsi and colleagues in 2000. In one of the two study groups, 25 men with variable duration of disease (2-15 months) were randomized to receive either 9 sessions of verapamil plus dexamethasone or placebo for a total of 3 weeks. After the initial 3 weeks of treatment, the placebo group then received 3 weeks of active treatment with verapamil [55]. This study found a significant improvement in pain, a decrease in the size of the plaque, but minimal change in penile deformity leading the group to conclude that EMDA offers a promising non-invasive option for the management of PD [55]. Levine and colleagues combined topical verapamil administration with EMDA and reported that

71% of patients had measurable verapamil levels in the tunica albuginea [56]. Although present, levels of verapamil found in the plaque was highly variable from barely detectable to as much as one-third of that which is found by direct injection.

Di Stasi and colleagues performed prospective, randomized study using EMDA with verapamil and dexamethasone in 2004, randomizing 96 men to either 5mg verapamil and 8 mg dexamethasone, or lidocaine (control) four times a week for 6 weeks [57]. The study reported that among the 76 patients that completed the study, absolute penile curvature improved by 22° versus 0° reduction in the control group ($p < .0001$), plaque volume decreased, and pain improved. However, a subsequent double-blind, placebo-controlled trial of 42 patients trial by Greenfield and colleagues comparing verapamil versus saline in electromotive drug administration for PD in 2007 found no significant difference with decreases in mean curvature change in experimental group was -9° vs -7° in control group at 3 months [58]. Another study randomized 60 men to receive either intralesional verapamil or EMDA of verapamil plus dexamethasone and found no statistically significant differences in penile deviation or plaque size [59]. The current guidelines for the management of Peyronie's disease recommend against the use of electromotive therapy with verapamil and further high quality randomized control trials are needed to evaluate the role of this therapeutic modality [1].

5.3 *Topical Liposomal Recombinant Human Superoxide Dismutase (LrhSOD)*

Topical Liposomal Recombinant Human Superoxide Dismutase (LrhSOD) is another investigational topical agent that has been characterized in one crossover trial and one observational study. Superoxide dismutase is a potent radical scavenger interrupting reactive oxygen species which are implicated in the inflammatory process responsible for plaque formation and the liposomal formulation allows for adequate tissue penetration in topical use. In an observational trial, Riedl and colleagues found that 25% of patients reported improvement in penile curvature, 56% reported plaque improvement, and 100% reported pain improvement [60]. In a double-blind cross-over study, 39 patients with PD and pain symptoms were treated with LrhSOD or placebo for a 4-week period [61]. Patients were then continued in a crossover model to ensure a total of 8 weeks of LrhSOD therapy for all participants. At week 12 pain was significantly reduced in 89% of patients who all had received 8 weeks of LrhSOD therapy at that

time. Response to other disease parameters was assessed at week 12: plaque size was reduced in 47% of patients, as was plaque consistence in 38%. Penile curvature was improved at 5–30 degrees in 23% of patients. Uncertainty remains regarding the efficacy of topical LrhSOD given the small body of evidence and small patient cohorts in current trials.

5.4 *H100 Gel*

There continues to be interest in investigating topical therapies for the management of Peyronie's disease. A new topical treatment called H-100, containing nifedipine and superoxide dismutase, using emu oil as a carrier agent, has been assessed by Twidwell and Levine in a randomized trial of 22 patients with acute phase PD and a mean curvature of approximately 50° [62]. Nifedipine is a calcium channel blocker as extracellular matrix and collagen formation is a calcium dependent process, and the mechanism of superoxide dismutase is discussed in section 4.3. Participants were randomly assigned to either a placebo or twice daily H-100 gel for 3 months. The study reported mean curvature reductions of 13.9° (27%) in the treatment group versus 1.2° (2.5%) in the control group. The mean improvement in curvature was 17° (37%) in patients who had used H-100 for 3 months and 20° (40%) in patients who had been using H-100 for 6 months. H-100 was well tolerated, and the trial only reported a self-limiting skin rash for toxicity. These results are promising, and further studies are needed to evaluate this therapy.

In conclusion, the current evidence for topical therapies is variable and there is a need for further investigation into their role in the management of PD. Clinical guidelines proposed by the AUA do not currently recommend any topical therapies [1]. In contrast, the EUA currently makes a "Grade B" recommendation on the use of 15% verapamil gel treatment for PD, although clinical trials as described in this review make it an unlikely choice of treatment [33].

6. Oral therapy

Treatment during the acute phase of Peyronie's disease may offer an opportunity to influence the disease's trajectory. While the inflammatory mechanisms behind the acute phase is an active area of research, this process ultimately promotes collagen synthesis and its deposition in the tunica albuginea. Clinically, this culminates into discrete regions of scarring, penile curvature and sexual dysfunction. In patients in the active phase with a degree of bother meeting the treatment

threshold, oral therapy has historically been an initial management option. Notably, the most recent guidelines from the AUA and EAU both discourage prescribing oral treatments for disease modifying intent, e.g. vitamin E, tamoxifen, procarbazine [1, 33]. Only NSAIDs are recommended by the AUA for analgesic purposes [1]. Recommendations against oral monotherapy are primarily due to the absence of strong evidence supporting their use; however, these agents continue to be offered to patients given low risk and potential benefits to scar formation, deformity, and pain (Table 2 for dosing of oral therapies).

6.1 *Pentoxifylline*

Pentoxifylline (PTX) is a non-specific phosphodiesterase (PDE) inhibitor with anti-fibrotic properties initially used in the transplant, cardiovascular, and dermatologic spaces [63-66]. Its mechanism involves several pathways such as improving peripheral tissue oxygenation, preventing platelet aggregation and release of cytokines, and inhibiting formation of free radicals [67]. Early andrological experience with PTX treatment observed stability or improvement in sonographic calcium burden and a reduced likelihood of subjective clinical deterioration [63]. While one randomized clinical trial (RCT) has been reported, these results were ultimately retracted due to concerns related to statistical analysis [68]. In one study, using PTX in combination with L-arginine and intralesional verapamil with or without traction, a penile curvature improvement of 20.9-26.9 degrees was observed [50]. Plaque reduction and improvement in erect penile curvature has been identified in subsequent investigations when PTX was used with combination with other oral therapies +/- penile traction therapy [69, 70]. The benign safety profile and potential benefits lend support the use of PTX in our own clinical protocol.

6.2 *Potassium para-aminobenzoate (POTABA™)*

Potassium para-aminobenzoate (POTABA™) elicits increased glycosaminoglycan and monoamine oxidase activity while decreasing collagen deposition with resulting restoration of normal extracellular matrix and decreased fibrosis. POTABA™ has been used in other inflammatory conditions including scleroderma and pulmonary fibrosis. Significant toxicities include gastrointestinal upset, fever, and rash. Randomized placebo-controlled trial in treatment-naive patients with a disease duration of < 12 months demonstrated decrease in plaque size [71].

Although no improvement in curvature was noted, POTABA™ did elicit a significant protective effect against progression of penile curvature compared to placebo (2.9 vs. 32.5%, $p = 0.001$) [71]. No analgesic benefit was observed. While use in the acute phase may slow the progression of penile curvature, widespread use of POTABA™ has not materialized due to gastrointestinal side effects.

6.3 *Colchicine*

Colchicine is a commonly used anti-gout medication that inhibits inflammation and collagen synthesis [72]. Initial studies demonstrated some promise to colchicine as a monotherapy; however, these benefits were not supported by results from a randomized trial. The first study in 1994 reported improvements in plaque burden, pain, and curvature in a sample of 24 patients treated with oral colchicine [73]. A subsequent prospective, observational investigation (N=60) elicited improvement in penile curvature in 30% of patients and stabilization in 48% when administered within 10 months of symptom onset [74]. However, prospective randomized trial data failed to demonstrate significant improvement in pain, curvature, or plaque size when initiated at a mean of 15 months following disease onset [75]. Interestingly, when administered in combination with vitamin E, one small trial comparing ibuprofen to vitamin E + colchicine observed a reduction in penile curvature and plaque size [76]. Overall, the evidence to support using colchicine is weak when administered as a monotherapy and favorable but limited when it is combined with vitamin E.

6.4 *Vitamin E*

Vitamin E (Tocopherol) is a fat-soluble, natural antioxidant, and the most commonly prescribed oral agent due to affordability, availability, and minimal toxicity. Vitamin E as a single agent has not been shown to be effective, and only anecdotally to improve patient perception of pain, although the effect does not differ significantly from observation alone [77-79]. RCT data of vitamin E added to multimodal therapy including other oral anti-inflammatory supplements (i.e. blueberries, propolis) and medications (i.e. diclofenac) and intralesional medications (i.e. verapamil) prevented plaque expansion, significantly improved curvature, and erectile function [69]. Vitamin E and colchicine in combination also has shown promise, as previously discussed [76]. Standard dosing is 400 IU one to two times daily, may provide added benefit when

combined with more invasive therapies, and possibly provide a psychological benefit to patients with minimal cost and toxicity. In spite of this we do not recommend use of vitamin E due to absence of data to show reduction of deformity.

6.5 *Tamoxifen*

Tamoxifen is a nonsteroidal estrogen receptor antagonist that was hypothesized to slow fibrosis by modulating TGF-beta secretion, an agent implicated in PD pathogenesis [80, 81]. Data are extremely limited, and the side effect profile is significant including hot flashes, erectile dysfunction, and thromboembolism. Prospective observational data in a small number of patients (n=36) shows 35.5% with improvement in curvature and plaque regression in 34.3% of patients with disease onset of less than 4 months [82]. Nonetheless, randomized controlled trial data, also in a small number of patients (n=25), failed to demonstrate any benefit when initiated at a mean of 20 months after disease onset in men without calcified plaques [83]. In the setting of poor tolerability and weak evidence to support its effectiveness, we do not recommend as routine medical therapy for Peyronie's disease.

6.6 *Carnitine*

Carnitine is an agent thought to be therapeutic in PD through its antioxidant effects (76) though its use is not supported by existing analyses [84]. A study evaluating acetyl-L-carnitine against tamoxifen in a single randomized study of patients both in the acute (<6 months) and chronic (>6 months) phase of disease showed that acetyl-L-carnitine was superior in preventing disease progression, relieving pain, and also reducing in plaque size [85]. Nonetheless, these results are difficult to interpret given the poor therapeutic value of tamoxifen and limited follow-up studies on acetyl-L-carnitine. A more recent trial also showed that neither propionyl-L-carnitine as a monotherapy nor in combination with vitamin E were effective for pain, curvature, or plaque burden compared to placebo [86].

6.7 *PDE-5 Inhibitors*

Lastly, PDE-5 inhibitors, while primarily used in the treatment of ED, exhibit anti-fibrotic activity through increased nitric oxide levels [87]. The administration of sildenafil has been shown to decrease plaque size and collagen/fibroblast ratio in rat models of PD. Vardenafil also

decreases collagen/smooth muscle & collagen III/I ratios, TGF-beta positive cells, myofibroblasts and rat plaque burden [88]. In a retrospective cohort study, Chung and colleagues evaluated the presence of septal scarring on penile ultrasound in 35 men treated with tadalafil 2.5 mg daily over 6 months to 30 untreated men. Patients treated with tadalafil had a higher proportion of septal scar resolution (69%) than the those in the control group (10%) [89]. Tadalafil in combination with extracorporeal shockwave therapy has been compared to shockwave therapy alone. In this randomized trial (N=100), patients receiving combined treatment had higher degrees of erectile function and quality of life but not curvature [90]. Although both groups did not have worsening of either plaque size and curvature, the value of tadalafil in this study is confounded by the use of shockwave therapy. Altogether, while PDE-5 inhibitors are well-tolerated and commonly used to treat ED concomitant with PD, higher quality data is necessary to assess their role in altering the pathophysiology of PD.

7. Conclusion

A variety of non-invasive and minimally invasive therapies exist for PD, but many options have been under-investigated and/or lacking in robust studies. For patients who are not indicated for or declining surgery, these interventions are an important treatment strategy for those with symptoms or bother. Intralesional collagenase remains the only FDA-approved treatment for PD but has been withdrawn from the market in the European Union, Canada and Australia. Many other therapies reviewed here, such as PTT and oral therapies, have been implemented into clinical practice, sometimes contrary to recommendations, due to their potential benefit and absence of risk. Because of the paucity of high-quality evidence, patients should be appropriately counseled about the risks and limitations of agents prior to initiation, especially those not recommended by professional guidelines.

8. Expert Opinion

Peyronie's disease arises from excessive collagen deposition in the tunica albuginea, resulting in plaque formation, erect penile deformity, and pain. Currently, intralesional collagenase is the only FDA-approved treatment for PD, but given varying degrees of evidence, there are many off-label treatments. When prescribing off-label therapies, providers should discuss the evidence as well as potential risks and benefits with patients. Among intralesional treatments, interferon α -2b

and verapamil remain off-label treatments but have conflicting data suggesting efficacy. Likewise, the data for ESWT is conflicting, and ESWT is currently approved for penile pain but does not provide durable responses for decreasing penile curvature or plaque size. Penile traction therapy can be effective in improving penile length, decreasing curvature, and increasing penile girth in areas of indentation, but the patient must wear the device consistently for at least 3-4 hours a day for several months to show clinical improvement, which may be a limiting factor. Topical therapies have not been shown to be effective, but topical verapamil is currently approved by the EAU. For oral agents, the data suggests limited efficacy for monotherapy for disease modifying intent, but combination treatments, such as verapamil, colchicine, and Vitamin E, show promise in improving Peyronie's disease. Overall, the multitude of treatment options, very few with strong evidence demonstrating consistent efficacy and reproducibility, opens the potential for further investigation with high quality trials as well as the possibility for multimodal treatment.

Further research must augment our understanding of PD pathophysiology, which may bring about new therapies or management approaches. Identification of molecular targets such as tissue inhibitors of matrix metalloproteinases (TIMPs), which regulate inflammation and subsequent fibrosis, as well as genetic markers will yield further targets for potential therapies [9, 91]. For example, genome wide association studies have identified several single nucleotide polymorphisms (SNPs) differentially regulated in Peyronie's disease, six of which are related to the WNT signalling pathway [92]. Furthermore, stem cell therapies may guide the development of novel oral or intralesional agents [93]. Biomarkers are needed to help predict those who may benefit from non-surgical treatment. Basic scientific research will be critical to providing insight on how we can best use our existing tools to treat PD and identify potential new therapies.

Clinically, we must also strengthen the evidence to help identify which of the existing options to support and which to discourage. Many studies in this space have small sample sizes, often lack control arms, and are retrospective in nature, making the data vulnerable to confounding variables and bias. Many therapies require high quality RCTs with large sample sizes, true controls, and objective, clinically meaningful outcomes to elucidate their therapeutic value as individual therapies. Furthermore, how we conduct PD studies must also be optimized, by

creating standardized protocols for measuring pre- and post-intervention assessments as well as creating a consensus as to what is considered a “clinically meaningful” change in the PD literature [94]. Additionally, some studies suggest that a multimodal approach may have improved efficacy compared to monotherapy, so we must also conduct high quality trials as agents may be synergistic and/or may sensitize the disease to other treatment modalities. Altogether, better understanding the pathophysiology of Peyronie’s disease will identify new targets for treatment as well as factors that may predict response to certain therapies, and higher quality trials on existing treatments for medical management of PD can better elucidate their therapeutic value.

Funding

This paper was not funded.

Declaration of Interest

L. Levine has declared consultancy for Boston Scientific, Coloplast, Absorption Pharmaceuticals, and Gesiva Medical. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

References

Paper of special note have been highlighted as () of interest, (**) of considerable interest*

1. Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's Disease: AUA Guideline. J Urol. 194, 745-53 (2019)*

These AUA guidelines highlight current medical and surgical treatments recommended for treatment of Peyronie's disease with comprehensive review of evidence.

2. Androustos G. [Francois Gigot de La Peyronie(1678-1747), benefactor of surgery and supporter of the fusion of medicine and surgery, and the disease that bears his name]. Prog Urol. 12(3), 527-33 (2002).
3. Musitelli S, Bossi M, Jallous J. A brief historical survey of "Peyronie's disease". J Sex Med 5(7), 1737-46 (2008).
4. Arafa M, Eid H, El-Badry A, et al. The prevalence of Peyronie's disease in diabetic patients with erectile dysfunction. Int J Impot Res 19(2), 213-7 (2007).
5. Dibenedetti DB, Nguyen D, Zografos L, et al. A Population-Based Study of Peyronie's Disease: Prevalence and Treatment Patterns in the United States. Adv Urol 2011:282503 (2011).
6. Moreland RB and Nehra A. Pathophysiology of Peyronie's disease. Internal Journal of Impotence research 14, 406-10 (2002).*

This publication reviews the concepts and various factors involved in the pathophysiology of PD, which is important in identifying potential therapeutic targets.

7. Somers KD, Dawson DM. Fibrin deposition in Peyronie's disease plaque. J Urol 1997; 157: 311 – 315.
8. Border WA, Ruoslahti E. Transforming growth factor-b in disease: the dark side of tissue repair. J Clin Inv 1992; 90: 1 – 7.
9. Del Carlo M, Cole AA, Levine LA. Differential calcium independent regulation of matrix metalloproteinases and tissue inhibitors of matrix metalloproteinases by interleukin-1beta and transforming growth factor-beta in Peyronie's plaque fibroblasts. J Urol. 179(6), 2447-55 (2008).
10. Kelly RB. Pathways of protein secretion in eukaryotes. Science 230, 25-32 (1985).
11. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. J Urol 151(6), 1522-4 (1994)
12. Levine LA, Goldman KE, Greenfield J. Experience with intraplaque injection of verapamil for Peyronie's disease. J Urol. 168, 621 (2002).

13. Shirazi M, Haghpanah AR, Badiie M, et al. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. *Int Urol Nephrol.* 41, 467-71 (2009)
14. Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long term single-blind study. *Urology.* 51, 620-6 (1998).
15. Bennett NE, Mulhall JP. Intralesional Verapamil Prevents the Progression of Peyronie's Disease. *J Urol.* 69(6), 1181-4 (2007)
16. Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. *J Urol* 158(4), 1395-9 1997)
17. Favilla V, Russo GI, Privitera S, et al. Combination of intralesional verapamil and oral antioxidants for Peyronie's disease: a prospective, randomized controlled study. *Andrologia.* 46, 936-42 (2014).
18. 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.* 25, 89-94 (1991).
19. Wegner HE, Andreson R, Knipsel HH, et al. Treatment of Peyronie's disease with local interferon-alpha 2b. *Eur Urol.* 28(3), 236-40 (1995).
20. Kendirci M, Usta MF, Matern RV, et al. The impact of intralesional interferon alpha-2b injection therapy on penile hemodynamics in men with Peyronie's disease. *J Sex Med.* 2(5), 709-15 (2005).
21. 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.* 176, 394-8 (2006).
22. Trost LW, Ates E, Powers M, et al. Outcomes of intralesional interferon- 2B for the treatment of Peyronie's disease. *J Urol.* 190, 2194-9 (2013).
23. Stewart CA, Yafi FA, Knoedler M et al. Intralesional Injection of Interferon-alpha2b improves Penile Curvature in Men with Peyronie's Disease Independent of Plaque location. *J Urol.* 194, 1704-7 (2015).
24. Gelbard MK, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. *Urol Res.* 10, 135-40 (1982).
25. Gelbard MK, Lindner A, Kaufman JJ. The use of collagenase in the treatment of Peyronie's disease. *J Urol.* 134, 280-3 (1985).

26. Gelbard MK, 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. 190, 199-207 (2013).**

This post-hoc analysis of 2 trials established that intralesional collagenase resulted in significant improvement in penile curvature and decreased overall PD symptom bother.

27. 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. 116(4), 650-6 (2015).

28. Hellstrom WJ, 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. 201(4):777-82 (2019).**

This cohort of 918 men showed significant dose-associated improvements in penile curvature and reinforced evidence for efficacy of intralesional collagenase for both acute/stable phase of PD.

29. Nguyen HMT, Anaissie J, DeLay KJ, et al. Safety and Efficacy of Collagenase Clostridium histolyticum in the Treatment of Acute-Phase Peyronie's Disease. J Sex Med 14(10), 1220-5 (2017).

30. Liu T, Shindel A, Lin G, et al. Cellular Signaling Pathways Modulated by Low-intensity Extracorporeal Shock Wave Therapy. Int J Impot Res 31(3), 170-6 (2019).

31. Wang CJ. Extracorporeal shockwave therapy in musculoskeletal disorders. J Orthop Surg Res. 7, 11 (2012).

32. Rassweiler JJ, Renner C, Chaussy C et al. Treatment of renal stones by extracorporeal shockwave lithotripsy: an update. Eur Urol. 39:187-99 (2001).

33. Hatzimouratidis K, Eardley I, Giuliano et al. EAU guidelines on penile curvature. Eur Urol. Eur Urol. 62, 543-52 (2012).

34. Bellorofonte C, Ruoppolo M, Tura M et al. [Possibility of using the piezoelectric lithotripter in the treatment of severe cavernous fibrosis]. Arch Ital Urol Nefrol Androl. 61, 417-22 (1989).

35. Abdel-Salam Y, Budair Z, Renner C et al. Treatment of Peyronie's disease by extracorporeal shockwave therapy: evaluation of our preliminary results. J Endourol 13, 549-52 (1999).

36. Palmieri A, Imbimbo C, Longo N, et al. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. Eur Urol. 56, 363-9 (2009).**

This is a high quality, prospective blinded clinical trial evaluating extracorporeal shockwave therapy and found that there was no significant improvement in plaque size/penile curvature.

37. Chitale S, Morsey M, Swift L, et al. Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. *BJU Int.* 106, 1352-6 (2010).
38. Hatzichristodoulou MC, Meisner C, Gschwend JE, et al. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. *J Sex Med.* 10, 2815-21 (2013).
39. Gao L QS, Qian S, Tang Z, et al. A meta-analysis of extracorporeal shock wave therapy for Peyronie's disease. *Int J Impot Res.* 28, 161-6 (2006).
40. Bekos A, Arvaniti M, Hatzimouratidis K et al. The natural history of Peyronie's disease: an ultrasonography-based study. *Eur Urol.* 53(3), 644-50 (2008).
41. Bella AJ, Lee JC, Grober ED, et al. 2018 Canadian Urological Association guideline for Peyronie's disease and congenital penile curvature. *Can Urol Assoc J.* 12, E197-209 (2018).
42. Bekos A, Arvaniti M, Hatzimouratidis K, et al. The natural history of Peyronie's disease: an ultrasonography-based study. *Eur Urol.* 53, 644-50 (2008).
43. Scropo FI, Mancini M, Maggi M, et al. Can an external penis stretcher reduce Peyronie's penile curvature? *Int J Impot Res.* 13, S21 (2001).
44. Lin H, Liu C, Wang R. Effect of Penile Traction and Vacuum Erectile Device for Peyronie's Disease in an Animal Model. *J Sex Med* 2017;14:1270–1276 .
45. Levine LA, Newell M, Taylor FL. Penile traction therapy for treatment of Peyronie's disease: A single-center pilot study. *J Sex Med.* 5(6), 1468-73 (2008).
46. Martínez-Salamanca JI, Egui A, Moncada I, et al. Acute phase peyronie's disease management with traction device: A nonrandomized prospective controlled trial with ultrasound correlation. *J Sex Med.* 11(2), 506-15 (2014).
47. Moncada KP, 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.* 123(4), 694-702 (2019).
48. 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.* 202(3):599-610 (2019).*

This cohort of 110 men demonstrated significant improvements in penile length/erectile function while reducing penile curvature and reported no significant adverse events with penile traction therapy.

49. Cowper MG, Burkett CB, Le TV, et al. Penile stretching as a treatment for Peyronie's disease: A review. *Sex Med Reviews*. 7(3), 508-15 (2019).
50. Abern MR, Larsen S, Levine LA. Combination of penile traction, intralesional verapamil, and oral therapies for peyronie's disease. . *J Sex Med*. 9(1), 288-95 (2011).
51. Martin DJ, Badwan K, Parker M, et al. Transdermal application of verapamil gel to the penile shaft fails to infiltrate the tunica albuginea. *J Urol*. 168(6):2483-5 (2002).
52. Lee RC. Calcium antagonists retard extracellular matrix production in connective tissue equivalent. *J Surg Res*. 49(5):463-6 (1990).
53. Fitch WP, Easterling WJ, Talbert RL, et al. Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of peyronie's disease--a placebo-controlled pilot study. *J Sex Med*. 4(2), 477-84 (2007).
54. Levine LA. Comment on 'Topical verapamil HCL, topical trifluoroperazine, and topical magnesium sulfate for the treatment of Peyronie's disease--a placebo-controlled pilot study'. *J Sex Med*. 4:1081-2 (2007).
55. Montorsi F, Salonia Guazzoni G, et al. Transdermal electromotive multi-drug administration for Peyronie's disease: preliminary results. *J Androl*. 21, 85-90 (2000).
56. Levine LA, Estrada CR, Shou W, et al. Tunica albuginea tissue analysis after electromotive drug administration. *J Urol*. 169(5), 1775-8 (2003)
57. Di Stasi SM, Giannantoni A, Stephen RL, et al. A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for peyronie's disease. *J Urol*. 171(4), 1605 (2004).
58. 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*. 177(3), 972-5 (2007).
59. Mehraei AR, Namdari F, Salavati A, et al. Comparison of transdermal electromotive administration of verapamil and dexamethasone versus intra-lesional injection for Peyronie's disease. *Andrology*. 1, 129-32 (2013).
60. Riedl CR, Plas E, Vorauer K, et al. Pilot study on liposomal recombinant human superoxide dismutase for the treatment of peyronie's disease. *Eur Urol*. 40(3), 343-9 (2001).

61. Riedl CR, Sternig P, Gallé G, et al. Liposomal recombinant human superoxide dismutase for the treatment of peyronie's disease: A randomized placebo-controlled double-blind prospective clinical study. *Eur Urol.* 48(4), 656-61 (2005).
62. Twidwell JL. Topical treatment for acute phase peyronie's disease utilizing a new gel, H-100: A randomized, prospective, placebo-controlled pilot study. *Int J Impot Rsearch.* 28(2), 41-5 (2016).
63. Smith JF, Shindel AW, Huang YC et al. Pentoxifylline treatment and penile calcifications in men with Peyronie's disease. *Asian J Androl.* 13:322-5 (2011).
64. McCarty MF. Interleukin-6 as a central mediator of cardiovascular risk associated with chronic inflammation, smoking, diabetes, and visceral obesity: down-regulation with essential fatty acids, ethanol and pentoxifylline. *Med Hypotheses.* 52, 465-77 (1997).
65. Noel C, Copin MC, Hazzan M, et al. Immunomodulatory effect of pentoxifylline during human allograft rejection: involvement of tumor necrosis factor-alpha and adhesion molecules. *Transplantation.* 69, 1102-7 (2000).
66. Tittelbach J, Graefe T, Wollina U. Painful ulcers in calciphylaxis - combined treatment with maggot therapy and oral pentoxifyllin. *J Dermatolog Treat.* 12, 211-4 (2001).
67. Annamaraju Pavan, Baradhi Krishna. Pentoxifylline. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559096/> Date accessed: Feb 28 2021.
68. Safarinejad MR, Asgari MA, Hosseini SY, et al. Retraction statement: A double-blind placebo-controlled study of the efficacy and safety of pentoxifylline in early chronic Peyronie's disease. *BJU Int.* 115, E10 (2015).
69. Paulis G, Brancato T, D'Ascenzo R, et al. Efficacy of vitamin E in the conservative treatment of Peyronie's disease: legend or reality? A controlled study of 70 cases. *Andrology.* 1, 120-8 (2013).
70. Gallo LS, Sarnacchiaro P. Ten-year experience with multimodal treatment for acute phase Peyronie's disease: A real life clinical report. *Actas Urol ESP.* 43:182-9 (2019).
71. Weidner W, Hauck EW, Schnitker J. Potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective, placebo-controlled, randomized study. *Eur Urol.* 47, 530-5 (2005).
72. El-Sakka AI, Bakircioglu ME, Bhatnagar RS, et al. The effects of colchicine on a Peyronie's-like condition in an animal model. *J Urol.* 161, 1980-3 (1999).
73. Akkus E, Carrier S, Rehman J, et al. Is colchicine effective in Peyronie's disease? A pilot study. *Urology.* 44, 291-5 (1994).

74. Kadioglu A, Tefekli A, Koksall T, et al. Treatment of Peyronie's disease with oral colchicine: long-term results and predictive parameters of successful outcome. *Int J Impot Res.* 12, 169-75 (2000).
75. Safarinejad MR. Therapeutic effects of colchicine in the management of Peyronie's disease: a randomized double-blind, placebo-controlled study. *Int J Impot Res.* 16, 238-43 (2004).
76. Prieto Castro RM, Leva Vallejo ME, Regueiro Lopez JC, et al. Combined treatment with vitamin E and colchicine in the early stages of Peyronie's disease. *BJU Int.* 91, 522-4 (2003).
77. Safarinejad MR, Hosseini SY, Kolahi AA, et al. Comparison of Vitamin E and Propionyl-L-Carnitine, Separately or in Combination, in Patients With Early Chronic Peyronie's Disease: A Double-Blind, Placebo Controlled, Randomized Study. *J Urol.* 178:1398-403 (2007).
78. Hashimoto K, Hisasue SI, Kato R et al. Outcome analysis for conservative management of Peyronie's disease. *Int J Urol.* 13, 244-7 (2006).
79. Lindsay MB, Schain DM, Grambsch P, et al. The incidence of Peyronie's disease in Rochester, Minnesota, 1950 through 1984. *J Urol.* 146, 1007-9 (1991).
80. Ralph DJ, Mirakian R, Pryor JP, et al. The immunological features of Peyronie's disease. *J Urol.* 155, 159-62 (1996).
81. Colletta AA, Wakefield LM, Howell FV, et al. Anti-oestrogens induce the secretion of active transforming growth factor beta from human fetal fibroblasts. *British Journal of Cancer.* 62, 405-9 (1990).
82. Ralph DJ, Brooks MD, Bottazzo GF, et al. The treatment of Peyronie's disease with tamoxifen. *Br J Urol.* 70, 648-51 (1992).
83. Teloken C, Rhoden EL, Grazziotin TM, et al. Tamoxifen versus placebo in the treatment of Peyronie's disease. *J Urol.* 162, 2003-5 (1999).
84. Vacante F, Senesi P, Montesano A, et al. L-Carnitine: An Antioxidant Remedy for the Survival of Cardiomyocytes under Hyperglycemic Condition. *J UDiabetes Res.* 2018, 4028297 (2018).
85. Calò L, Pagnin E, Davis PA et al. Antioxidant effect of l-carnitine and its short chain esters: Relevance for the protection from oxidative stress related cardiovascular damage. *International Journal of Cardiology.* 107, 54-60 (2006).
86. Biagiotti G, Cavallini G. Acetyl-L-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. *BJU Int.* 88, 3-7 (2001).
87. Gonzalez-Cadavid NF, Rajfer J. Treatment of Peyronie's disease with PDE5 inhibitors: an antifibrotic strategy. *Nat Rev Urol.* 7, 215-21 (2010).

88. Valente EG, Vernet D, Ferrini MG, et al. L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and related fibroblast cultures. *Nitric Oxide*. 9, 229-44 (2003).
89. Chung E, DeYoung L, Brock GB. The Role of PDE5 Inhibitors in Penile Septal Scar Remodeling: Assessment of Clinical and Radiological Outcomes. *J Sex Med*. 8, 1472-7 (2011).
90. Palmieri A, Imbimbo C, Creta M, et al. Tadalafil once daily and extracorporeal shock wave therapy in the management of patients with Peyronie's disease and erectile dysfunction: results from a prospective randomized trial. *Int J Androl*. 353, 190-5 (2012).
91. Gokce A, Abd Elmageed ZY, Lasker GF, et al. Intratunical Injection of Genetically Modified Adipose Tissue-Derived Stem Cells with Human Interferon alpha-2b for Treatment of Erectile Dysfunction in a Rat Model of Tunica Albuginea Fibrosis. *J Sex Med*. 12(7), 1533-44 (2015).
92. Dolmans GH, Werker PM, de Jong IJ, et al. WNT2 Locus Is Involved in Genetic Susceptibility of Peyronie's Disease. *J Sex Med* 9, 1430-4 (2009). doi:10.1111/j.1743-6109.2012.02704.x.
93. Moussa M, Chakra MA, Moussa Y. Advances in stem cell therapy for treatment of Peyronie's disease. *Intractable Rare Dis Res* 9(1), 10-13 (2020). doi: [10.5582/irdr.2019.01130](https://doi.org/10.5582/irdr.2019.01130) *
- This review highlights advances in stem cell therapy, specifically adipose derived stem cells (ADSCs) as a potential new therapy to promote tissue repair and treat penile fibrosis from PD.
94. Ziegelmann MJ, Trost LW, Russo GI et al. Peyronie's Disease Intervention Studies: An Exploration of Modern-Era Challenges in Study Design and Evaluating Treatment Outcomes. *J Sex Med*. 17(3), 364-77 (2020).

Table 1: Summary of intralesional studies for PD

Agent	Study	Cohort	Outcome
Verapamil	Levine et al 1994	N=14	Reduction of >50% in plaque volume in 30%, stable or improved plaque in 83%
	Levine et al 2002	N=156	84% w/ resolution of pain. 60% improved penile curvature with mean 31°
			Reduction of plaque size 17.5% treatment vs 12.8% control (p=0.75).
	Shirazi et al	N=80	Pain 30% treatment vs 28.2% control (p=0.99) Curvature 17.5% treatment vs 23.1% control (p=0/86)
	Rehman et al	N=14	Reduced plaque size 57% treatment vs 28% control (p<0.04), penile curvature w/ absolute improvement 8% (p<0.07).
Interferon α -2b	Wegner et al	N=25	76% (19/25) stable or improved plaque. Mean absolute improvement in curvature 12° (48.8° pre-treatment vs 36.8° post-treatment). Significant improvements in plaque size/pain
	Kendirci et al	N=39	
	Hellstrom et al 2006	N=117	Mean plaque size absolute improvement (2.6 vs 0.9 cm ²) (p<0.01), mean penile curvature 13.5 ° vs 4.5 degrees (p<0.01)
	Trost et al	N=127	54% w/ improvement, mean improvement 9 degrees
	Stewart et al	N=131	91% response rate, Improvement in dorsal curvature 8.7° vs. ventral curvature 9.3°, p=0.84
CCH	Gelbard et al 2013	N=832	34% improvement in penile curvature, 17 ° treatment vs 9.3 ° control. Penile curvature <30°= Improvement 14.8° in treatment group vs 7.6° control p<0.001. 61-90° curvature= Improvement 25° in treatment group vs 17° control. Significant improvement IIEF score, PD symptom bother score
	Lipschultz et al	N=832	
	Hellstrom et al 2019	N=918	17° improvement in curvature, 74.4% patients with >20% improvement in curvature

Table 2: Dosage of oral drugs for Peyronie's Disease

Oral Drug	Dose
Pentoxifylline	400 mg TID
Potassium para-aminobenzoate (POTABA)	12 g daily
Colchicine	1-2 mg daily
Vitamin E	200-300 mg daily
Tamoxifen	20 mg daily
Carnitine	1 g BID
Tadalafil	2.5 mg daily

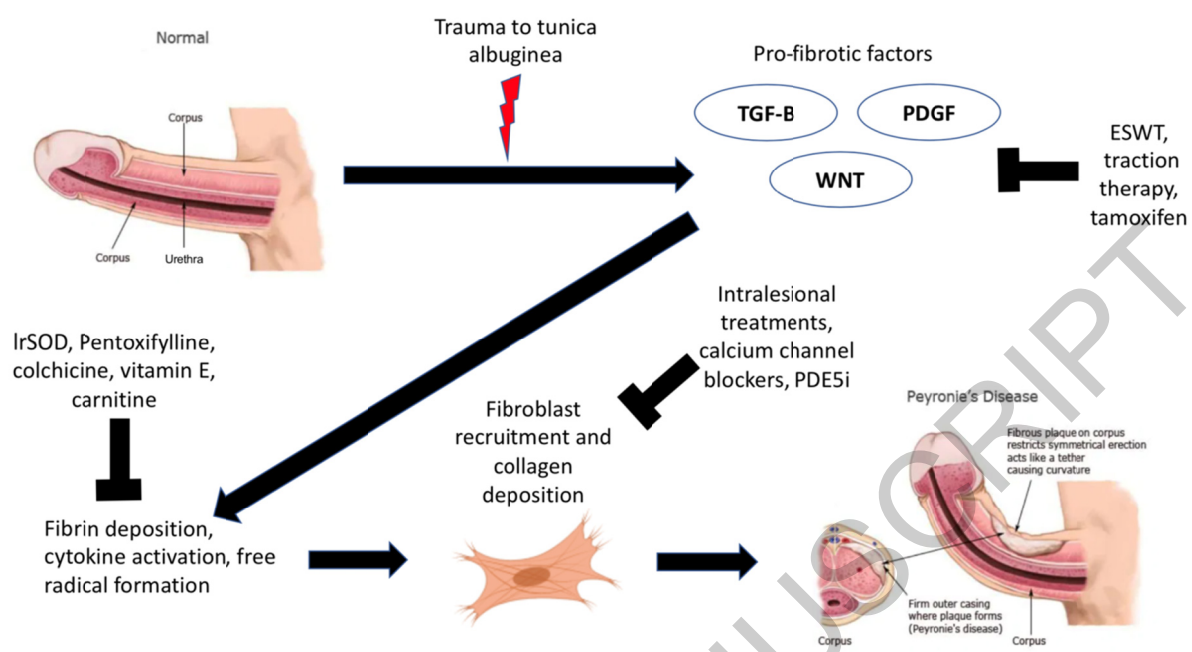


Fig 1