Current Urology Reports (2021) 22: 6
https://doi.org/10.1007/s11934-020-01024-8

MEN'S HEALTH (R CARRION, SECTION EDITOR)

Conservative Therapy for Peyronie's Disease: a Contemporary Review of the Literature

Ayad Yousif[1] · Caleb Natale[1] · Wayne J. G. Hellstrom[1]

Accepted: 23 November 2020 / Published online: 8 January 2021

Abstract

Purpose of Review To analyze the literature on current conservative treatment options for Peyronie's disease (PD).

Recent Findings Conservative therapy with intralesional collagenase clostridium histolyticum (CCH) is safe and efficacious in either the acute or chronic phases of PD. Combination treatment with penile traction therapy (PTT) can produce even better results. While most PTT devices require extended periods of therapy up to 8 h per day, the RestoreX® device can be effective at 30–90 min per day.

Summary A variety of conservative therapies are available for treatment of PD. The available literature does not reveal any treatment benefit of oral therapies. Intralesional therapy is the mainstay conservative treatment of PD. Intralesional CCH therapy is the first Food and Drug Administration-approved intralesional therapy and represents the authors' preference for medical therapy. The most effective conservative management of PD likely requires a combination of therapies.

Keywords Peyronie's disease · Conservative therapy · Oral therapy · Intralesional therapy · Mechanical therapy

Introduction

Peyronie's disease (PD) is a connective tissue disorder characterized by the formation of fibrotic plaque in the tunica albuginea of the corpus cavernosa. Definitive etiology of the disease remains elusive. The most accepted theory involves repetitive microtrauma of the tunica albuginea with delamination of this layer, followed by hematoma formation and initiation of an inflammatory cascade [1]. PD is mostly diagnosed in men in the fifth decade of life; however, patients younger than 40 account for 10% of PD cases [2]. Though there is concern that PD is likely underreported, as patients may be hesitant to seek treatment, the reported prevalence of PD is 0.5-20% [3–5].

Clinical presentation is variable and may include erectile dysfunction (ED), pain, penile shortening, deformity, curvature, and penile plaque formation [2]. Clinically, two phases of PD are recognized: the acute phase and the chronic phase [6]. In the acute phase, which typically lasts up to 12 months, patients complain of painful erection, progressive penile curvature, and palpable plaque(s). In the chronic phase, the plaque(s) solidifies, the pain subsides, and penile curvature stabilizes. Patients suffering from PD may suffer from psychological distress in addition to affected sexual function.

The goal of therapy is to mitigate pain or discomfort, reduce penile curvature, improve sexual performance, and improve appearance. Surgery is the gold-standard treatment for reducing penile curvature. However, there is a paucity of data concerning surgical intervention in the acute phase of disease and thus the American Urological Association (AUA) guidelines suggest that surgery not be pursued until the stable phase is reached, typically 12–18 months after symptom onset [7•]. In most men, conservative therapy is effective in relieving pain and preventing the progression of the disease during the acute phase. One or more trials of conservative treatment may also be warranted in the stable phase of disease prior to surgery, as potential surgical complications include shortened penile length and ED. This communication aims to review the latest updates in the nonsurgical treatment of PD.

Oral Therapy

There is limited evidence that oral therapies are effective in treatment of PD, and the AUA, European Association of

This article is part of the Topical Collection on *Men's Health*

✉ Wayne J. G. Hellstrom
whellst@tulane.edu

[1] Department of Urology, Tulane University School of Medicine, 1430 Tulane Ave. 86-42, New Orleans, LA 70112, USA

Urology (EAU), and International Consultation on Sexual Medicine (ICSM) guidelines recommend avoiding oral treatments [7•, 8•, 9]. Though oral therapies may be useful as adjunctive medications in select patients or in patients who refuse other therapies, they should not delay more effective treatment [10]. The authors do not recommend oral agents as first-line PD therapy unless there are other indications for the product's use.

Potassium Aminobenzoate (Potaba)

Potaba was initially established as a treatment for PD after it was suggested that potaba can reduce collagen formation [11]. In 2005, Weidner conducted a prospective, randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy of potaba in the treatment of PD [12]. He concluded that potaba may reduce plaque size and halt the progression of penile deformity, with no improvement noted in penile curvature.

A more recent retrospective study of 109 PD patients included 44 who received potaba. The majority of participants in the potaba arm dropped out prior to 6 months, mainly due to gastrointestinal side effects and lack of efficacy [13]. There was no statistically significant improvement in penile pain, plaque size, or penile curvature. These findings are in line with previous literature that concludes potaba lacks efficacy and is associated with high dropout rate due to side effects [8•]. Although rare, acute liver injury is a recorded side effect of potaba use [14].

Vitamin E

Vitamin E is a fat-soluble vitamin that was discovered in 1922 through experimentation involving sterile rats [15]. Vitamin E has antioxidant activity that inhibits reactive oxygen species and protects cell membrane against lipid peroxidation [16]. The first report of vitamin E use in PD was in 1948 by Scott and Scardino [17]. This was followed by a number of studies on vitamin E and other PD treatments, with mixed results.

In a double-blind, placebo-controlled, randomized study on 236 patients, Safarinejad demonstrated that vitamin E or vitamin E plus propionyl-L-carnitine showed no statistically significant changes in penile curvature, plaque size, or penile pain relief [18]. Conversely, a smaller prospective study of 25 patients who received 1200 mg of vitamin E on a daily basis reported that 16 patients displayed improvement in penile angulation with a mean curvature reduction of 21°, although these patients also received 3–6 sessions of extracorporeal shock wave lithotripsy (ESWL) at 1-week intervals [19].

Several studies have illustrated statistically significant, albeit modest, effectiveness of vitamin E in conjunction with other treatments, including verapamil, topical diclofenac [20], multiple antioxidants, and pentoxifylline [21]. The variable effect of vitamin E as a potential treatment option in PD should be carefully explained. Although it is not recommended by the AUA or the EAU, vitamin E was the second most common oral medicine prescribed by specialists treating PD across Europe [22]. Noted side effects are rare, but may include cerebrovascular events, gastrointestinal distress, and headache [10].

Pentoxifylline

Pentoxifylline (PTX) is a non-specific inhibitor of phosphodiesterases that is used in vascular perfusion disorders. PTX attenuates fibroblast proliferation and inhibits elastogenesis and collagen production [23]. In a double-blind, randomized-controlled trial, 228 patients were randomized to a PTX group ($n = 114$) and a control group ($n = 114$). After 6 months, patients in the PTX group showed significant improvement in penile curvature and a reduction in plaque size. In comparison to the placebo group, PTX-treated patients also reported significant improvement in sexual function, as indicated by higher International Index of Erectile Function (IIEF) scores and peak systolic velocities by on penile duplex Doppler study [24].

PTX has often been studied as a treatment for PD in conjunction with other therapies. In a prospective quasi-experimental study of 46 patients to evaluate the efficacy of PTX and/or colchicine with penile traction, 27 patients received PTX 400 mg twice daily for 6 months. Improved penile curvature and plaque size were observed in these patients, as well as increased peak systolic velocity [25]. In another controlled study, the therapeutic effect of PTX in combination with other antioxidants plus or minus intralesional PTX injections was assessed in 307 patients. Improvement in penile curvature was reported in 96.8%, 56.4%, and 3.6% of patients receiving the injection protocol, patients receiving the non-injection protocol, and the control group, respectively. Reduction in plaque volume and penile pain was statistically significant in both treatment groups [26]. A 2019 retrospective study of 177 patients being treated for PD reported reduced disease progression, as measured by no significant increase in erect penile curvature before and after 6 months of treatment, with PTX and L-arginine combined oral therapy [27]. The addition of intralesional verapamil injections and penile traction therapy to this regimen resulted in a significant reduction in penile curvature.

PTX is a cheap and well tolerated medicine with minimal side effects and relatively strong clinical evidence of a potential therapeutic role in patients with PD. The AUA [7•] and EAU [8•] have opted to not recommend PTX due to the lack of repeated randomized trials.

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 inhibitors (PDE5i) are commonly used to treat ED. These medications have also been studied as alternative therapy for PD. The proposed mechanism suggests efficacy in PD through downregulation of collagen I synthesis and induction of apoptosis that eliminates fibroblasts and myofibroblasts [28]. These effects are mediated by the inhibition of PDE5 and the maintenance of high cGMP levels and activation of protein kinase G (PKG), which reduce collagen synthesis by downregulating transforming growth factor-beta1 (TGF-β1) expression [28].

The antifibrotic role of PDE5i was demonstrated in 2011 in a study in which 35 patients with isolated septal scars received a daily dose of 2.5 mg tadalafil for 6 months. A majority (69%) reported diminishment of their septal scar and higher IIEF-5 scores [29]. In another study, 39 patients were divided into two groups: 18 received 400 IU vitamin E per day, and 21 received 50 mg sildenafil daily for 12 weeks. Patients who received sildenafil reported significant improvement in IIEF score and reduced penile pain and plaque size. The authors concluded that the daily administration of PDE5i may have therapeutic value in PD patients [30].

In a recent PD rat model, a combination of PDE5i (vardenafil) and a selective estrogen receptor modulators (tamoxifen) demonstrated more antifibrotic activity than with each drug alone. The antifibrotic effect is mediated through collagen gel contraction and inhibition of myofibroblast transformation and TGF-β1–induced extracellular matrix protein production [31]. Additional studies have also reported improved outcomes with combination therapy, including by pairing a PDE5i with ESWT and collagenase clostridium histolyticum (CCH) [32–34].

Other

No randomized-controlled trial has evaluated the efficacy of L-arginine, a commercially available supplement, as a monotherapy; however, L-arginine has demonstrated promising results when combined with other modalities of treatment, as mentioned previously [27].

Additional oral therapies trialed to mitigate symptoms of PD include carnitine, colchicine, omega-3, and coenzyme Q. However, little if any evidence exists supporting the effectiveness of these other treatments.

Topical Treatment

Topical treatments for PD have been trialed due to the noninvasive nature of drug application. However, there is no sufficient evidence that topical application can deliver adequate levels of active compound to the region of interest [35]. Given this limitation, and the lack of large, control trial data concerning topical treatments for PD, topical therapy is not recommended by the AUA [7•], EAU [8•], or ICSM [9] guidelines, and the authors of this communication do not utilize these products.

Verapamil

Studies have reported that verapamil, a calcium channel blocker, has the dose-dependent ability to inhibit fibroblast proliferation and synthesis and secretion of extracellular matrix molecules and decrease platelet-derived growth factor BB-dependent collagen deposition in the extracellular matrix. Verapamil also increases the proteolytic activity of collagenase and suppresses TGF-β1 activity [36, 37].

In 2002, Martin et al. sought to assess the infiltration of topically applied verapamil into the tunica albuginea. They applied verapamil to the penile shafts of men the night before and morning of scheduled penile prosthesis surgery for treatment of ED. Tunical specimens were obtained intraoperatively and verapamil tissue level was measured, with no verapamil noted in any of these samples [35].

In a later pilot study, Fitch et al. compared topical verapamil 15% gel to topical trifluoperazine and topical magnesium sulfate [38]. After 9 months of treatment, patients in the topical verapamil arm experienced 61.1%, 84.7%, and 100% improvement in penile curvature, plaque change, and pain resolution, respectively; however, this study has a number of limitations including the discontinuation of trifluoperazine and lack of objective measures [38].

H-100

H-100 gel combines the calcium channel blocker nicardipine and a free-radical scavenger superoxide dismutase with Emu oil, a natural carrier agent. Emu oil is thought to be an efficacious transdermal carrier due to its high content of fatty acids to aid in delivery of active agents to the tunica albuginea [39]. A 2016 prospective, randomized, double-blinded, placebo-controlled study reported significant improvement in outcomes including mean stretched penile length, mean curvature reduction, and mean pain reduction in the 11 patients treated with H-100 compared to the 11 controls at 6 months [40]. Results are limited by the small size of this study and the questionable methodology for measuring penile curvature.

Electromotive Drug Administration

Electromotive drug administration (EMDA) represents a minimally invasive method to deliver drugs into deep tissue layers using an electrical current created between two electrodes. Three events involved in the electromotive transport are,

namely, iontophoresis, electroosmosis/electrophoresis, and electroporation.

Two studies evaluated the efficacy of verapamil delivered through EMDA in the treatment of patients with PD. In the first study, 96 patients were randomized to receive verapamil and dexamethasone vs. 2% lidocaine, via EMDA. The electrodes were applied for 20 min, four sessions/week for 6 weeks. In the 37 patients who completed the study, significant improvement in plaque volume and penile curvature was documented in the study group, while the volume and curvature were unchanged in the control group. All patients experienced transient skin reaction [41].

In 2006, Levine conducted a double-blind, placebo-controlled trial to determine the effectiveness of verapamil delivered through EMDA. A total of 23 patients were randomized to the verapamil treatment group and 19 were randomized to the saline group. Patients received treatment twice weekly for 3 months. Improvement in penile curvature was not statistically significant in either group [42].

Intralesional Injections

Injection of active agents into penile plaques allows for local action of pharmacologically active agents at higher concentrations than can be delivered by oral or topical routes. Intralesional agents have proven more effective than oral or topical agents but must be injected at each treatment. Intralesional therapies are the mainstay medical treatment in PD [43]. Recent population-based research suggests that injectable therapies may be displacing surgical therapy [44]. Our practice routinely utilizes intralesional agents, particularly CCH, for first-line treatment of PD (Fig. 1).

Verapamil

In 1994, Levine conducted the first study to evaluate the efficacy of intralesional verapamil in the treatment of penile plaque(s) [45]. This study was followed by two prospective nonrandomized studies [46, 47]. The largest was in 2002 and included 140 patients [47]. After 12 weeks of treatment, objective improvement in penile curvature was noted in 60% of patients. A total of 83% of patients demonstrated increased girth, and 71% reported improved sexual function.

In 1998, Rehman et al. reported a randomized single-blind placebo-based study involving 14 patients randomized into two groups: verapamil vs. saline. Treatments were administered intralesionally, weekly for 6 months. The verapamil group reported significantly decreased plaque length, width, and volume as well as improved quality of erections. There was a trend in penile curvature improvement, although this change was not significant. None of these reported metrics was significantly changed in the control group. All

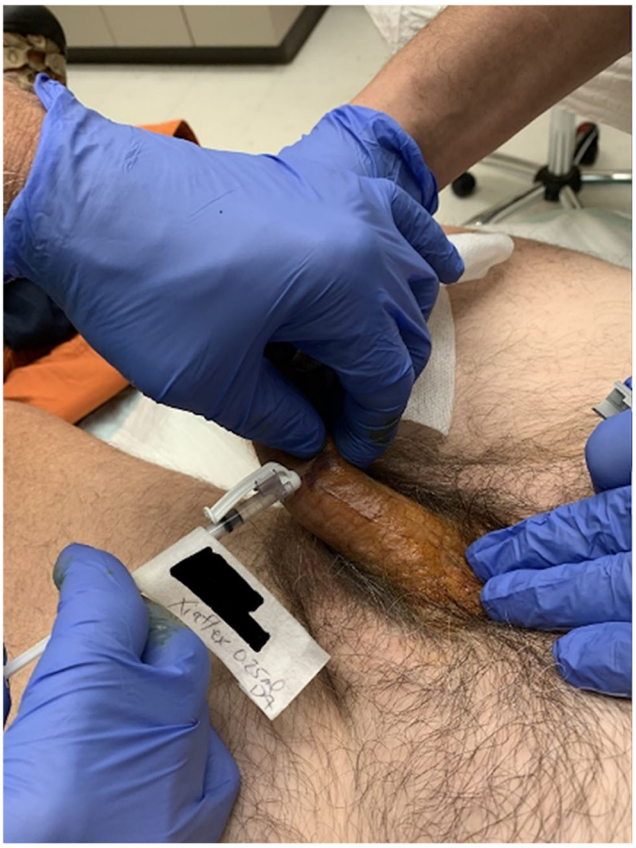

Fig. 1 Application of intralesional collagenase clostridium histolyticum

verapamil-treated patients demonstrated softening of the plaque. The authors stated that patients were more likely to benefit from surgery if the initial angulation was > 30° or the patient showed no response to intralesional verapamil after 3 months of treatment [37].

The results of the above studies were contradicted by Shirazi et al. in a randomized single-blind placebo-controlled trial. Patients were divided into two groups, 40 in the verapamil arm and 40 in the saline arm. No statistically significant improvement was noted in the verapamil arm regarding plaque size, pain, curvature, plaque softening, or sexual function [48].

In 2016, Favilla compared intralesional verapamil to intralesional hyaluronic acid (HA) in a prospective, double-blinded, randomized study of two groups. The first group included 69 patients receiving intralesional verapamil weekly for 12 weeks. In the second group, 63 patients received intralesional HA weekly for 12 weeks. Both groups reported improved plaque size and sexual satisfaction; however, changes in penile curvature and overall patients' sexual satisfaction were more prominent in the HA group [49]. These discrepancies among the studies could be attributed to differences in patient selection, plaque calcification, injection technique, and drug concentration.

A 2018 systematic review of seven randomized and two nonrandomized studies evaluating the clinical efficacy of verapamil, including those listed above, concluded that available evidence did not support use of verapamil injections or meaningful improvement in penile curvature [50••]. This view is in line with AUA guidelines [7•], while EAU guidelines [8•] and ICSM guidelines [9] offer a conditional recommendation for intralesional verapamil treatment.

Interferons

Interferons (IFNs) are a large family of naturally occurring cytokines secreted by host immune cells in response to viral infections, tumors, and other biological inducers as diverse counter measures against immune stimulation. IFN has antifibrotic activity that induces a dose-dependent inhibition of fibroblast proliferation on fibroblast cultured from diseased penile plaque. Also, it inhibits collagen production and increases collagenase production [51].

The first placebo-controlled trial of intralesional injection therapy for PD was reported in 2006 [52]. A total of 117 patients were randomized to receive either IFN α-2b or saline (10 ml) biweekly for 12 weeks (six injections). This study demonstrated that intralesional IFN α-2b therapy is effective and resulted in significant improvement in measured parameters. Resolution of pain in the IFN α-2b group was higher than in the placebo group (67.7% and 28.1%, respectively). Mean improvement in penile curvature was 27.01% in the IFN α-2b group vs. 8.87% in the control group. Additionally, the IFN α-2b group showed significant increase in the peak systolic velocity, which may explain the improvement in sexual function. The authors postulated that the injected volume of saline can exert a local effect that remodels the plaque. These results were reproduced by a retrospective study of 127 IFNα-2b patients, wherein 54% of patients showed an overall 9° improvement in penile curvature. Response to treatment was not related to the age of the patient, initial penile curvature, nor the duration of the disease [53]. In a more recent study, the authors concluded that intralesional IFN α-2b was safe and effective in patients with ventral curvature with similar outcomes compared to dorsal plaques [54]. Systematic review found IFN α-2b therapy to be effective in improving penile curvature and reducing plaque size [50••]. The authors utilize IFN as first-line therapy in patients who are not eligible for CCH therapy.

Collagenase

Collagenase clostridium histolyticum (CCH) (Xiaflex®, Endo Pharmaceuticals, Malvern, PA) constitutes a fixed ratio of collagenase I and II (AUX-I : AUX-II). It is an injectable agent that enzymatically degrades collagen within the penile plaque. CCH is an effective nonsurgical treatment of PD that can be used as a singular therapy or in conjunction with other treatment options [55]. Although most of the available research has concerned stable phase disease, CCH is appropriate in both the acute and stable phases, according to more recent literature [55] (Table 1). High degree of calcification within plaques is a relative contraindication for intralesional CCH [63].

Gelbard et al. first demonstrated the effectiveness of CCH in degrading penile plaques in 1982 [64]. In 2013, the safety and efficacy of CCH in the treatment of PD were illustrated with two large, prospective, multi-institutional, double-blind, randomized, placebo-controlled studies [56]. The IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) trials I and II included 832 men with PD, from 64 sites across the USA and Australia. Inclusion criteria were penile curvature > 30° and < 90° and a duration of PD of more than 12 months. Patients with ventral curvature, duration of disease less than 12 months, refractory ED, or calcified plaque were excluded.

There was a 34% improvement in penile curvature (− 17.0 ± 14.8°) in the CCH-treated arm compared to the 18.2% improvement in the placebo arm (− 9.3 ± 13.6°). Additionally, the authors documented significant improvement in Peyronie's Disease Questionnaire (PDQ) symptom bother score in the CCH-treated men. Treatment-related adverse events were encountered in 84% of patients, although these were mostly mild or moderate in severity and the majority (79%) resolved without intervention within 1-2 weeks. In 2013, collagenase became the first Food and Drug Administration (FDA)-approved treatment for PD.

Levine then conducted a phase 3, open-label multicenter study of 347 patients that adopted the same treatment protocol of the IMPRESS trial. The results of this study reinforced the results of the IMPRESS trials [57].

Long-term efficacy and safety of CCH therapy were assessed in a very recent phase 4 study that included 280 patients, of which 204 completed the study [58•]. Inclusion criteria involved men who received CCH treatment in either 12-month, double-blind, placebo-controlled clinical trials (IMPRESS I/II), or one of two 9-month open-label studies. At 5-year follow-up, it was noted that 180 patients showed an additional 9.1% improvement in penile curvature compared with reference data. Also, patients showed additional significant improvement in PDQ bother domain mean score. This study reports the sustained long-term improvement in penile curvature and bother symptoms in patients treated with CCH therapy.

A retrospective study by Nguyen illustrated the efficacy and safety of CCH to treat acute phase PD. A total of 162 patients were included in this review, in which 36 enrolled in the acute-phase PD arm and 126 patients were enrolled in the stable-phase PD arm. There was no statically significant difference noted between the two groups in the improvement

Table 1 Selected contemporary studies supporting use of collagenase clostridium histolyticum for Peyronie's disease management in patient populations

Population	Study	Cohort	Treatment	Outcome	Significance
Stable phase	Gelbard et al. [56]	832 men	IMPRESS trials protocol	34% improvement in penile curvature (− 17.0 ± 14.8°) at 52 weeks compared to 18.2% improvement (− 9.3 ± 13.6°) in placebo	$p < 0.0001$
	Levine et al. [57]	347 men	IMPRESS trials protocol	34.4% (95% CI − 37.6%, − 31.2%) improvement in penile curvature (− 18.3 ± 14.0°) at 36 weeks	Significant on 95% CI
	Goldstein et al. [58•]	280 men, 204 completed	Follow-up study, previous IMPRESS protocol	180 patients showed additional 9.1% improvement in penile curvature (− 4.3 ± 13.4°) at 5 years compared to end of previous study	$p < 0.02$
Acute phase	Nguyen et al. [59]	162 men: 83% stable phase, 17% acute phase	Retrospective, IMPRESS protocol	Final change in curvature was 16.7° and 15.6° for the acute and stable phase PD groups. The difference in treatment-related adverse events not significant (11% acute vs. 10% stable phase).	$p = 0.654$ $p = 0.778$
	Hellstrom et al. [60••]	918 men	Retrospective, IMPRESS protocol with modifications	30.1% improvement in penile curvature (− 14.5 ± 14.0°) overall after the fourth or last (< 4) cycle. Acute/stable phase not significant in predicting curvature improvement of at least 20%.	$p < 0.0001$ $p > 0.05$
Ventral/atypical curvature	Alom et al. [61]	228 patients	Prospective, IMPRESS protocol with modifications	49.1% improvement in penile curvature (− 29.5°, SD = 22.2) for ventral curvature compared to 38% (− 11.4°, 13.9) and 25% (− 15.0°, 16.7) for lateral and dorsal curvatures, respectively	$p < 0.01$ for all groups compared to baseline
	Cocci et al. [62]	65 men	Shortened protocol	Median penile curvature change of − 20.0° (IQR: − 20.0 to − 10.0°), − 20.0° (− 20.0 to 0°), and − 15.0° (− 15.0 to − 15.0°) in the ventral, hourglass, and shortening groups, respectively	$p < 0.01$ for all groups compared to baseline

IMPRESS Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies

of penile curvature (16.7 vs. 15.6; $p = .654$), nor in the frequency of adverse events. Although CCH treatment was not previously recommended in the acute phase of PD, this study emphasizes the safety and efficacy of intralesional collagenase in acute phase PD [59].

Results from a large multi-institutional study (the "Real World Trial") were comparable to findings of previous studies: CCH is as safe and efficacious in the acute phase of PD [60••]. The study retrieved retrospective data from five high-volume centers and included 918 patients; 17% were in the acute phase of the disease, characterized by history of PD of 6 months or less, and 83% were in the stable phase. There was no difference in response to CCH treatment in both acute and stable phases, indicating safety and efficacy of collagenase in the acute setting. Additionally, this study illustrated that the number of cycles was predictive of curvature improvement, where 73% of patients who completed four cycles of treatment experienced a 20% improvement in penile deformity [60••]. In 2017, Raheem et al. proposed a modified protocol for intralesional CCH injection. The study included 53 patients who received three intralesional injections of 0.9 mg of CCH, at 4-week intervals. A total of 51 patients showed improvement in penile curvature of 17.3° or 31.4% from the baseline. Although the results of the shortened protocol were comparable to the IMPRESS trials, the study was nonrandomized and of a small sample size by a single investigator [65•].

Patients with ventral curvature were excluded from the IMPRESS trial, due to the concern of urethral injury. Alom et al. conducted a prospective cohort of 228 patients from March 2014 through March 2018 in which 25, 189, and 115 patients had ventral, dorsal, and lateral curvature, respectively. IMPRESS protocol for intralesional injection was followed. Ventral and lateral curvature showed greater relative response compared to the dorsal curvatures (ventral 29.5°, lateral 11.4°, and dorsal 15.0°, respectively) [61]. A smaller retrospective study which included 53, 7, and 5 patients with ventral, hourglass, and shortening curvature, respectively, found that treatment response was not significantly impacted by penile curvature [62]. Median curvature change was 20.0°, 20.0°, and 15.0° for the ventral, hourglass, and shortening groups respectively.

CCH can be used as a monotherapy or combined with additional therapies for superior results [55]. These include oral sildenafil therapy [33], percutaneous needle tunneling [66], and vacuum and penile traction devices [55, 67]. Current EAU recommendations suggest that CCH is a safe and effective alternative to surgery in stable disease and can be considered an optional treatment in active disease [8•], while AUA guidelines suggest administration of intralesional CCH can be utilized in combination with modeling in patients with stable disease [7•] (Table 2). Although rare, the feared complication of CCH therapy in PD is tunical rupture, which requires a distinct treatment protocol from traumatic penile fracture [68]. We currently use intralesional CCH in patients with stable or acute phase PD with significant penile curvatures.

Mechanical Therapy

The use of traction in PD is to realign collagen fibrils parallel to the axis of tension. These changes can be induced by a process called mechano-transduction in which mechanical stimuli are translated into chemical signals and by decreased myofibroblast activity [69].

Penile Traction Therapy

Several studies evaluated penile traction therapy (PTT) as a monotherapy or part of combination regimen, with oral or intralesional injections. Most of these studies demonstrated improvement in penile curvature and stretched penile length.

A recent randomized-controlled trial evaluated PD patients treated with the novel RestoreX® (Pathright Medical, Plymouth, MN) device. In comparison to other devices, RestoreX can be applied for 30–90 min daily and achieve counter bending in four directions. In the study, 110 participants were randomized 1:3 into (a) control group or (b) RestoreX penile traction group for 30 min once, twice, or 3 times/day. There was significant improvement in penile curvature and length when compared to the control. IIEF-Erectile Function domain recorded significantly improved sexual function in patients [70].

Evidence for use of PTT in combination with intralesional injection has been mixed. A 2019 analysis of a prospective registry reported improved penile curvature reduction, penile length, and subjective curvature improvement with the RestoreX device and CCH therapy than in patients treated with either CCH monotherapy or CCH therapy in conjunction with other traction devices [71]. Mean curvature improvement was 33.8° for the RestoreX group, compared to 20.3° and 19.2° for the CCH monotherapy and CCH + other traction device groups, respectively. This study did not show significant additional benefit of the non-RestoreX traction devices when used in combination with CCH.

Ziegelmann et al. prospectively studied 35 men treated with and 16 treated without PTT during CCH injection therapy [72•]. All but one of the traction group patients used the Andropenis® (Andromedical America-Asia, New York, NY). Patients were instructed to apply traction for a minimum 3 h daily. The study reported no significant differences in degree of curve improvement or stretched penile length between the two groups. An earlier study of patients treated with or without PTT with the Andropenis during IFNα-2b injection therapy found a significantly increased stretched penile length in patients who completed 3 or more hours of PTT per day compared to those who did not use PTT [73]. On meta-analysis, men who used PTT showed a statistically longer stretched penile length compared to men

Table 2 Summary of recommendations by organization for intralesional injection therapies in the management of Peyronie's disease

Intralesional agent	AUA Peyronie's Disease 2015	EAU Sexual and Reproductive Health 2020	ICSM Peyronie's Disease 2016
Verapamil	Clinicians may offer intralesional verapamil for the treatment of patients with PD.	Intralesional treatment with verapamil and nicardipine is no longer recommended due to contradictory results.	Intralesional verapamil injection therapy has some outcome benefits in PD management.
Recommendation	Conditional, Evidence Strength C	None, Evidence level 1b	Grade C, Evidence Level 3
Interferon α-2b	Clinicians may administer intralesional interferon α-2b to patients with PD.	Interferon α-2b may be offered in patients with stable curvature dorsal or lateral > 30°.	Intralesional interferon therapy has some outcome benefits in PD management.
Recommendation	Moderate, Evidence Strength C	Strong	Grade B, Evidence Level 2
Collagenase clostridium histolyticum (CCH)	CCH [may be administered] with modeling…in patients with stable PD, penile curvature > 30° and < 90°, intact erectile function.	Intralesional therapy with CCH may be offered in patients with stable PD and dorsal/lateral curvature > 30^0.	Intralesional collagenase injection has shown outcome benefits in PD management.
Recommendation	Moderate, Evidence Strength B	Strong	Grade B, Evidence Level 2

AUA American Urological Association; *EAU* European Association of Urology; *ICSM* International Consultation on Sexual Medicine

who did not use PTT after primary intervention, although this difference was small [74•].

Most of these penile traction devices (with the exception of RestoreX) need to be applied for an extended period of time (up to 8 h daily), which could affect patient compliance. No comparative studies are available to compare success, patient compliance, and treatment-related side effects. However, compared to surgery and CCH, the RestoreX device was the most cost-effective treatment [75•]. The AUA and EAU provide weak and no recommendation for traction therapy use, respectively, citing limited evidence and small sample sizes [7•, 8•]. In our practice, penile traction devices have been used to effectively reduce curvature, generally combined with intralesional CCH therapy. However, results are dependent on adherence to device application protocol and only the most motivated patients have been able to observe optimal results.

Vacuum Device

The clinical application of the vacuum device in the treatment of PD was evaluated in a single-armed study of 31 patients. Patients were instructed to use the vacuum device, without the constriction ring, for 10 min twice daily over a 12-week period. An improvement in penile curvature of between 5 and 25° was noted in 21 patients. Additionally, patients experienced increase in penile length between 0.5 and 1.5 cm ($p = 0.029$) and diminished penile pain. No statistically significant changes were noted in erectile function. This study suggests vacuum device can induce straightening of penile deformity by applying mechanical stretch therapy [76].

Vacuum devices have the benefit of low morbidity and the noninvasive nature of device application, although the effectiveness of vacuum device in treating PD is still not well documented [77]. AUA and EAU guidelines suggest that vacuum devices may be offered as part of a multimodal therapy approach for penile deformity reduction, although this recommendation is weak [8•]. We do not generally use this device in our practice for this purpose.

Extracorporeal Shock Wave Therapy

Two mechanisms are hypothesized for the therapeutic mechanism of low intensity extracorporeal shock wave therapy (LiESWT) in patients with PD: direct damage and remodeling of the penile plaque, and heat-induced angiogenesis with subsequent inflammation that prompts plaque lysis via macrophages [78].

Four randomized-controlled trials examined LiESWT in the treatment of PD [79–82]. None of these studies showed a significant improvement in penile plaque size or penile curvature; however, treated subjects showed a significant reduction in penile pain.

In one open-label single-arm prospective study, 30 patients received 3000 shock waves twice weekly for 6 weeks [34]. A third of the patients showed improvement of penile curvature between 15 and 60° and decreased penile plaque size in 27% of patients. Six patients reported penile pain prior to therapy, while four reported pain resolution during LiESWT therapy. These changes were persistent at 3-month follow-up. The author attributes these findings to the use of a newer generation of shock wave lithotripter that induces plaque disruption without underlying cavernosal damage. Additionally, more complex PD cases were not included in this study. A 2019 multicenter single-arm study assessed the effectiveness of LiESWT in 325 consecutive patients treated with ESWT for PD [83•]. Patients received one treatment per week during the 3-month protocol. At 3 months, the study reported significant reductions in median plaque size and penile curvature, as well as increased median erect penile length and IIEF and improved PDQ subdomains. The AUA [7•] and EAU guidelines [8•] suggest that shockwave therapy can be used to treat penile pain in the acute phase of PD, although its use is inappropriate for treating penile curvature or plaque size. We do not utilize this therapy in our practice in accordance with the Sexual Medicine Society of North America (SMSNA) position statement [84], which states that this therapy is experimental and should be used only under research protocols.

Radiotherapy

Due to anti-inflammatory action of radiotherapy, a retrospective study reviewed 83 patients treated with 8 fractions of 4 Gy in the early stages of PD [85]. Mean follow-up was 52 months. The authors reported that 47% of patients have symptom regression compared to 7% of patients who showed disease progression. The authors concluded that radiation therapy for PD was safe and well-tolerated, particularly in pain relief. However, available data does not support penile curvature improvement [86].

Radiotherapy is not recommended in PD, owing to the risk of ED due to smooth muscle atrophy, and neuronal and vascular damage [87].

Conclusion

Many studies have been conducted in order to establish a strategy founded on evidence-based medicine to treat PD. Conservative treatment may still be an attractive choice for many patients who wish to avoid surgical treatment. Both oral and topical treatments have not demonstrated therapeutic efficacy in the majority of studies, either due to small sample size, lack of control arm, or unreproducible results. Intralesional injections have demonstrated more meaningful results, especially when combined with other modalities of treatment. CCH is the first FDA-approved intralesional treatment in PD, with proven efficacy based on randomized, double-blind, placebo-controlled studies. Most of the studies recommend LiSWT to relieve penile pain, but with no effect on penile curvature or plaque size. As per the SMSNA position statement, it is considered experimental and should be not be used in clinical practice. Effective conservative management of PD likely requires a combination of the therapies described here. Overall, prospective randomized trials are needed to better understand the mechanism of PD and to evaluate response to different conservative therapeutic options.

Compliance with Ethical Standards

Conflict of Interest Dr. Wayne Hellstrom is on a speakers' bureau for Endo Pharmaceuticals and was a principal investigator on the IMPRESS and "Real World" trials. No other author reports any conflict of interest.

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

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Devine CJ Jr, et al. Proposal: trauma as the cause of the Peyronie's lesion. J Urol. 1997;157:285–90.
2. Sharma KL, Alom M, Trost L. The etiology of Peyronie's disease: pathogenesis and genetic contributions. Sex Med Rev. 2020;8(2):314–23. https://doi.org/10.1016/j.sxmr.2019.06.004.
3. Dibenedetti DB, Nguyen D, Zografos L, Ziemiecki R, Zhou X. A population-based study of Peyronie's disease: prevalence and treatment patterns in the United States. Ther Adv Urol. 2011;2011:282503–9. https://doi.org/10.1155/2011/282503.
4. Schwarzer U, Sommer F, Klotz T, Braun M, Reifenrath B, Engelmann U. The prevalence of Peyronie's disease: results of a large survey. BJU Int. 2001;88(7):727–30.
5. Chung E, Gillman M, Rushton D, Love C, Katz D. Prevalence of penile curvature: a population-based cross-sectional study in metropolitan and rural cities in Australia. BJU Int. 2018;122(Suppl 5):42–9.
6. Hussein AA, Alwaal A, Lue TF. All about Peyronie's disease. Asian J Urol. 2015;2(2):70–8. https://doi.org/10.1016/j.ajur.2015.04.019.
7.• • Nehra A, Alterowitz R, Culkin DJ, et al. Peyronie's disease: AUA guideline. J Urol. 2015;194(3):745–53. https://doi.org/10.1016/j.juro.2015.05.098. **A systematic review of the literature was performed to create guidelines pertinent to the diagnosis and treatment of Peyronie's disease. AUA recommendations are based on consensus of scientific evidence.**

8.• • EAU Guidelines. Edn. presented at the EAU Annual Congress Amsterdam. 2020. ISBN 978–94–92671-07-3. **A systematic review of the literature was performed to create guidelines pertinent to the diagnosis and treatment of Peyronie's disease. EAU recommendations are based on consensus of scientific evidence.**
9. Chung E, Ralph D, Kagioglu A, Garaffa G, Shamsodini A, Bivalacqua T, et al. Evidence-based management guidelines on Peyronie's disease. J Sex Med. 2016;13(6):905–23. https://doi.org/10.1016/j.jsxm.2016.04.062.
10. Brimley SC, Yafi FA, Greenberg J, Hellstrom WJG, Tue Nguyen HM, Hatzichristodoulou G. Review of management options for active-phase Peyronie's disease. Sex Med Rev. 2019;7(2):329–37. https://doi.org/10.1016/j.sxmr.2018.09.007.
11. Zarafonetis CJ, Horrax TM. Treatment of Peyronie's disease with potassium para-aminobenzoate (potaba). J Urol. 1959;81:770–2.
12. Weidner W, Hauck EW, Schnitker J, et al. Potassium paraaminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective, placebo-controlled, randomized study. Eur Urol. 2005;47:530–5.
13. Park TY, Jeong HG, Park JJ, Chae JY, Kim JW, Oh MM, et al. The efficacy of medical treatment of Peyronie's disease: potassium para-aminobenzoate monotherapy vs. combination therapy with tamoxifen, L-carnitine, and phosphodiesterase type 5 inhibitor. World J Mens Health. 2016;34(1):40–6.
14. Al Attar L, Kilgore W. Rare incidence of acute liver injury with potassium para-aminobenzoate introduction. Case Rep Gastroenterol. 2018;12(2):230–3 Published 2018 May 31.
15. Evans HM, Bishop KS. On the existence of a hitherto unrecognized dietary factor essential for reproduction. Science. 1922;56(1458):650–1.
16. Sikka SC, Hellstrom WJ. Role of oxidative stress and antioxidants in Peyronie's disease. Int J Impot Res. 2002;14(5):353–60.
17. Scott WW, Scardino PL. A new concept in the treatment of Peyronie's disease. South Med J. 1948;41:173–7.
18. Safarinejad MR, Hosseini SY, Kolahi AA. 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. 2007;178(4 Pt 1):1398–403 discussion 1403.
19. Claro JA, Passerotti CC, Figueiredo Neto AC, Nardozza A Jr, Ortiz V, Srougi M. An alternative non-invasive treatment for Peyronie's disease. Int Braz J Urol. 2004;30(3):199–204.
20. Paulis G, Brancato T, D'Ascenzo R, de Giorgio G, Nupieri P, Orsolini G, et al. Efficacy of vitamin E in the conservative treatment of Peyronie's disease: legend or reality? A controlled study of 70 cases. Andrology. 2013;1(1):120–8.
21. 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;9:129–39. Published 2017 Jul 20. https://doi.org/10.2147/RRU.S141748.
22. Porst H, Burri A, European Society for Sexual Medicine (ESSM) Educational Committee. Current strategies in the management of Peyronie's disease (PD)-results of a survey of 401 sexual medicine experts across Europe [published correction appears in J Sex Med. 2019 Sep;16(9):1486]. J Sex Med. 2019;16(6):901–8.
23. Shindel AW, Lin G, Ning H, Banie L, Huang YC, Liu G, et al. Pentoxifylline attenuates transforming growth factor-β1-stimulated collagen deposition and elastogenesis in human tunica albuginea-derived fibroblasts part 1: impact on extracellular matrix. J Sex Med. 2010;7(6):2077–85.
24. Safarinejad MR, Asgari MA, Hosseini SY, Dadkhah F. A double-blind placebo-controlled study of the efficacy and safety of pentoxifylline in early chronic Peyronie's disease [retracted in: Safarinejad MR, Asgari MA, Hosseini SY, Dadkhah F. BJU Int. 2015 Mar;115(3):E10]. BJU Int. 2010;106(2):240–8.
25. Ibrahim A, Gazzard L, Alharbi M, Rompré-Brodeur A, Aube M, Carrier S. Evaluation of oral pentoxifylline, colchicine, and penile traction for the management of Peyronie's disease. Sex Med. 2019;7(4):459–63.
26. Paulis G, Barletta D, Turchi P, et al. Efficacy and safety evaluation of pentoxifylline associated with other antioxidants in medical treatment of Peyronie's disease: a case-control study. Res Rep Urol. 2015;8:1–10 Published 2015 Dec 31.
27. Gallo L, Sarnacchiaro P. Ten-year experience with multimodal treatment for acute phase Peyronie's disease: a real life clinical report. Diez años de experiencia con el tratamiento multimodal de la fase aguda de la enfermedad de Peyronie: reporte médico de la vida real. Actas Urol Esp. 2019;43(4):182–9. https://doi.org/10.1016/j.acuro.2018.08.005.
28. Valente EG, Vernet D, Ferrini MG, Qian A, Rajfer J, Gonzalez-Cadavid NF. L-arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and related fibroblast cultures. Nitric Oxide. 2003;9(4):229–44.
29. 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. 2011;8(5):1472–7.
30. Ozturk U, Yesil S, Goktug HN, et al. Effects of sildenafil treatment on patients with Peyronie's disease and erectile dysfunction. Ir J Med Sci. 2014;183(3):449–53.
31. Ilg MM, Mateus M, Stebbeds WJ, Milenkovic U, Christopher N, Muneer A, et al. Antifibrotic synergy between phosphodiesterase type 5 inhibitors and selective oestrogen receptor modulators in Peyronie's disease models. Eur Urol. 2019;75(2):329–40.
32. Farrell MR, Ziegelmann MJ, Levine LA. Minimally invasive therapies for Peyronie's disease: the current state of the art. Transl Androl Urol. 2020;9(Suppl 2):S269–83. https://doi.org/10.21037/tau.2019.08.06.
33. Cocci A, Cito G, Urzì D, Minervini A, di Maida F, Sessa F, et al. Sildenafil 25 mg ODT + collagenase Clostridium hystoliticum vs collagenase Clostridium hystoliticum alone for the management of Peyronie's disease: a matched-pair comparison analysis. J Sex Med. 2018;15(10):1472–7. https://doi.org/10.1016/j.jsxm.2018.08.012.
34. Chung E. Peyronie's disease and low intensity shock wave therapy: clinical outcomes and patient satisfaction rate in an open-label single arm prospective study in Australian men. Korean J Urol. 2015;56(11):775–80.
35. Martin DJ, Badwan K, Parker M, Mulhall JP. Transdermal application of verapamil gel to the penile shaft fails to infiltrate the tunica albuginea. J Urol. 2002;168(6):2483–5.
36. Anderson MS, Shankey TV, Lubrano T, Mulhall JP. Inhibition of Peyronie's plaque fibroblast proliferation by biologic agents. Int J Impot Res. 2000;12(Suppl 3):S25–31.
37. 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):620–6.
38. Fitch WP 3rd, Easterling WJ, Talbert RL, Bordovsky MJ, Mosier M. Topical verapamil HCl, topical trifluoperazine, and topical magnesium sulfate for the treatment of Peyronie's disease-a placebo-controlled pilot study. J Sex Med. 2007;4(2):477–84.
39. Qiu XW, Wang JH, Fang XW, Gong ZY, Li ZQ, Yi ZH. Di Yi Jun Yi Da Xue Xue Bao. 2005;25(4):407–10.
40. Twidwell J, Levine L. Topical treatment for acute phase Peyronie's disease utilizing a new gel, H-100: a randomized, prospective, placebo-controlled pilot study [published correction appears in Int J Impot Res. 2020 Jun 2]. Int J Impot Res. 2016;28(2):41–5. https://doi.org/10.1038/ijir.2015.22.
41. 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. 2004;171(4):1605–8.

42. 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):972–5.
43. Aliperti LA, Mehta A. Peyronie's disease: intralesional therapy and surgical intervention. Curr Urol Rep. 2016;17(9):60. https://doi.org/10.1007/s11934-016-0622-2.
44. Sukumar S, Pijush DB, Brandes S. Impact of the advent of collagenase Clostridium histolyticum on the surgical management of Peyronie's disease: a population-based analysis. J Sex Med. 2020;17(1):111–6. https://doi.org/10.1016/j.jsxm.2019.09.022.
45. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. J Urol. 1994;151:1522–4.
46. Levine LA. Treatment of Peyronie's disease with intralesional verapamil injection. J Urol. 1997;158:1395–9.
47. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. J Urol. 2002;168:621–5; discussion 625–626.
48. 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;41:467–71.
49. Favilla V, Russo GI, Zucchi A, Siracusa G, Privitera S, Cimino S, 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):771–5.
50.•• •• Russo GI, Milenkovic U, Hellstrom W, Levine LA, Ralph D, Albersen M. Clinical efficacy of injection and mechanical therapy for Peyronie's disease: a systematic review of the literature. Eur Urol. 2018;74(6):767–81. https://doi.org/10.1016/j.eururo.2018.07.005. **This systematic review includes evidence synthesized from available literature. The study reported that there is sufficient evidence to suggest that CCH and IFNα-2b injection therapy have a clinically significant effect on improving penile curvature and conserving penile length. There was no sufficient evidence to support the use of other injection and mechanical treatments for PD.**
51. 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;25:89–94.
52. Hellstrom WJG, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon α-2b for minimally invasive treatment for Peyronie's disease. J Urol. 2006;176(1):394–8.
53. Trost LW, et al. Outcomes of Intralesional Interferon-α2B for the Treatment of Peyronie Disease. J Urol. 2013;190(6):2194–9.
54. Stewart CA, 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):1704–7.
55. Natale C, McLellan DM, Yousif A, Hellstrom WJG. Review of intralesional collagenase Clostridium histolyticum injection therapy and related combination therapies in the treatment of Peyronie's disease (an update) [published online ahead of print, 2020 Mar 18]. Sex Med Rev. 2020;S2050–0521(20):30009–3. https://doi.org/10.1016/j.sxmr.2020.01.005.
56. 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;190:199–207.
57. Levine LA, Cuzin B, Mark S, Gelbard MK, Jones NA, Liu G, et al. Clinical safety and effectiveness of collagenase Clostridium histolyticum injection in patients with Peyronie's disease: a phase 3 open-label study. J Sex Med. 2015;12:248–58.
58.• • Goldstein I, 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):1191–7. **This phase-4 study included men previously enrolled in either the IMPRESS trials or the open-label studies of CCH. While 280 patients were included in the study, only 204 completed the study. Of these, 180 showed additional penile curvature improvement at 5-year follow-up. Patients also showed improvement in PDQ bother domain mean score. This study reports sustained long-term improvement in penile curvature in patients treated with CCH therapy at 5-year follow-up without further CCH treatment.**
59. 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. 2017;14:1220–5.
60.•• •• Hellstrom WJG, 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):777–82. **First large, multi-institutional study which occurred at institutions where the IMPRESS trial was instituted for the routine treatment of PD. This study reported no difference in response to CCH therapy in the acute vs. stable phases of PD. This study also illustrated that number of cycles was predictive of curvature improvement.**
61. Alom M, et al. Safety and efficacy of collagenase Clostridium histolyticum in Peyronie's disease men with ventral curvatures. Urology. 2019;129:119–25.
62. Cocci A, Di Maida F, Russo GI, et al. How atypical penile curvature influence clinical outcomes in patients with Peyronie's disease receiving collagenase Clostridium histolyticum therapy? World J Mens Health. 2020;38(1):78–84. https://doi.org/10.5534/wjmh.190026.
63. Masterson TA, Rezk A, Ramasamy R. Characteristics predictive of response to collagenase Clostridium histolyticum for Peyronie's disease: a review of the literature. World J Urol. 2020;38(2):279–85. https://doi.org/10.1007/s00345-019-02850-3.
64. Gelbard MK, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. Urol Res. 1982;10:135–40.
65.• • Abdel Raheem A, Capece M, Kalejaiye O, et al. Safety and effectiveness of collagenase Clostridium histolyticum (CCH) (Xiapex®) in the treatment of Peyronie's disease using a new modified shortened protocol. BJU Int. 2017;120(5):717–23. **In this prospective study of 53 subjects at a single center, patients underwent a shortened, nonrandomized protocol of 3 CCH injections at 4-week intervals in combination with manual modeling, stretching, and vacuum device on a daily basis. Reported results were similar to those of the IMPRESS trials, indicating that a shortened protocol may be appropriate in some patients.**
66. Fernández-Pascual E, González-García FJ, Angulo J, Cerezo E, Quintana LM, Turo J, et al. Optimizing collagenase Clostridium histolyticum therapy for Peyronie's disease using a novel approach with percutaneous needle tunnelling. BJU Int. 2019;124(6):1055–62. https://doi.org/10.1111/bju.14784.
67. García-Gómez B, García-Rojo E, Alonso-Isa M, et al. Treatment of Peyronie's disease with combination of Clostridium histolyticum collagenase and penile traction therapy: a prospective, multicenter, single-arm study [published online ahead of print, 2020 May 4]. Int J Impot Res. 2020. https://doi.org/10.1038/s41443-020-0292-y.
68. Hughes W, Natale C, Hellstrom WJG. The management of penile fracture: a review of the literature with special consideration for patients undergoing collagenase Clostridium histolytica injection therapy. Curr Urol Rep. 2020; (In Press).
69. Alenghat FJ, Ingber DE. Mechanotransduction: all signals point to cytoskeleton, matrix, and integrins. Sci STKE. 2002;2002(119):pe6.

70. 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.
71. Alom M, Sharma KL, Toussi A, Kohler T, Trost L. Efficacy of combined collagenase Clostridium histolyticum and RestoreX penile traction therapy in men with Peyronie's disease. J Sex Med. 2019;16(6):891–900. https://doi.org/10.1016/j.jsxm.2019.03.007.
72.• • Ziegelmann MJ, Viers BR, Montgomery BD, Avant RA, Savage JB, Trost LW. Clinical experience with penile traction therapy among men undergoing collagenase Clostridium histolyticum for Peyronie disease. Urology. 2017;104:102–9. https://doi.org/10.1016/j.urology.2017.01.054. **In this randomized-controlled trial of 110 patients with PD and curvature of 30° or greater, patients were assigned to either 30 or 90 min of traction therapy per day with the RestoreX device. The study reported significant improvement in penile curvature and length in those treated with the traction device compared to the control group. Time for traction therapy treatment in this study was significantly shorter than is typically required.**
73. Yafi FA, Pinsky MR, Stewart C, Sangkum P, Ates E, Trost LW, et al. The effect of duration of penile traction therapy in patients undergoing intralesional injection therapy for Peyronie's disease. J Urol. 2015;194(3):754–8. https://doi.org/10.1016/j.juro.2015.03.092.
74.• • Haney NM, Kohn TP, Nichols PE, Hellstrom WJ. 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;122:110–5. https://doi.org/10.1016/j.urology.2018.07.039. **This systematic review evaluated 4 studies, and 348 total patients, which included penile traction therapy as an adjunct treatment for PD. On meta-analysis, there was a significantly greater stretched penile length in men treated with traction therapy after their primary intervention compared to those not treated with penile traction. This improvement was not significantly different in the surgical vs. injection therapy subgroups.**
75.• • Wymer K, Kohler T, Trost L. Comparative cost-effectiveness of surgery, collagenase Clostridium histolyticum, and penile traction therapy in men with Peyronie's disease in an era of effective clinical treatment. J Sex Med. 2019;16(9):1421–32. **This cost analysis determined that RestoreX traction therapy was the most cost-effective treatment compared to surgery and CCH therapy.**
76. Raheem AA, Garaffa G, Raheem TA, Dixon M, Kayes A, Christopher N, et al. The role of vacuum pump therapy to mechanically straighten the penis in Peyronie's disease. BJU Int. 2010;106:1178–80.
77. Cowper MG, Burkett CB, Le TV, Scherzer N, Hellstrom WJG. Penile stretching as a treatment for Peyronie's disease: a review. Sex Med Rev. 2019;7(3):508–15. https://doi.org/10.1016/j.sxmr.2018.11.002.
78. Lingeman JE, McAteer JA, Kempson SA, Evan AP. Bioeffects of extracorporeal shock wave lithotripsy: strategy for research and treatment. Urol Clin North Am. 1988;15:507–14.
79. Palmieri A, Imbimbo C, Longo N, Fusco F, Verze P, Mangiapia F, 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. 2009;56:363–70.
80. Chitale S, Morsey M, Swift L, Sethia K. Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. BJU Int. 2010;106:1352–6.
81. Palmieri A, Imbimbo C, Creta M, Verze P, Fusco F, Mirone V. 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. 2012;35:190–5.
82. Hatzichristodoulou G, Meisner C, Gschwend JE, Stenzl A, Lahme S. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. J Sex Med. 2013;10:2815–21.
83.• • 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):339–46. https://doi.org/10.5534/wjmh.180100. **In this single-arm, multi-institutional study, 325 consecutive patients were treated with ESWT for PD. The authors reported significant reductions in median plaque size and penile curvature, as well as increased median erect penile length and IIEF and improved PDQ subdomains.**
84. Sexual Medicine Society of North America. Position statement: ED restorative (Regenerative) therapies (shock waves, autologous platelet rich plasma, and stem cells). 27 March, 2018. PDF: https://www.smsna.org/V1/images/SMSNA_Position_Statement_RE_Restorative_Therapies.pdf. Accessed 25 Sept 2020.
85. Pietsch G, Anzeneder T, Bruckbauer H, et al. Superficial radiation therapy in Peyronie's disease: an effective and well-tolerated therapy. Adv Radiat Oncol. 2018;3(4):548–51. Published 2018 Aug 7. https://doi.org/10.1016/j.adro.2018.07.009.
86. Tsambarlis P, Levine LA. Nonsurgical management of Peyronie's disease. Nat Rev Urol. 2019;16(3):172–86. https://doi.org/10.1038/s41585-018-0117-7.
87. Mahmood J, Shamah AA, Creed TM, et al. Radiation-induced erectile dysfunction: recent advances and future directions. Adv Radiat Oncol. 2016;1(3):161–9 Published 2016 Jun 3.