Peyronie's Disease Non-Surgical Treatment

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Key Points:

1. Treatment selection should consider patient priority and phase of the disease (Figure 1), and men should be provided realistic expectations of outcomes.
2. Patients with active/unstable Peyronie's Disease (PD) may be offered reassurance, NSAID's ,or shock wave treatment (SWT) for the treatment of pain. Patients should be counseled that SWT has not been shown to improve penile deformity.
3. A patient with stable disease and minimal bother does not warrant additional treatment beyond reassurance. Curvature assessment with intracavernosal injection should be performed in the office for stable phase patients considering treatment.
4. Intralesional collagenase Clostridium histolyticum (CCH) is the only drug with FDA approval for the treatment of PD, and is indicated in men with adequate erectile function, with dorsal or lateral curvature of 30-90 degrees. (Table 2)
5. The following treatments should be avoided: oral vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, L-carnitine, electromotive topical verapamil, radiotherapy.

Key words

Peyronie's, bent penis, curved penis, penile plaque, penile pain, penile scar tissue, collagenase, clostridium, xiaflex™, intralesional injection, penile shortening.

1. Introduction

A variety of oral, mechanical and injectable therapies have been utilized in the management of Peyronie's Disease (PD). While many non-surgical options for PD are based on sound scientific rationale, few are supported by well-designed, double blind, placebo controlled, randomized trials.

There are several obstacles that make it difficult to decipher PD clinical trials.[2,3]

Few trials enroll enough patients to attain sufficient power. Meta-analysis is difficult because of the heterogeneity of treatments and duration of follow-up, as well as the variety of study endpoints that are documented[4] Because the goal of intervention largely revolves around the stabilization or correction of penile deformity, it is critical that studies perform objective curvature measurements before and after intervention. Unfortunately, this careful measurement is not universal in published studies of PD therapy.

The ideal study in PD **utilizes objective, uniform means of deformity assessment, pain, and sexual function, including ability to achieve penetration for patients who desire this outcome** Clinically meaningful endpoints are critical; vague endpoints such as "decrease in curvature" are undermined if the patient remains unable to engage in satisfying sexual relations, or if the patient still requires surgical intervention because of inadequate improvement. Although there are reliable and reproducible assessments available to characterize PD in individual patients, they are not consistently used in clinical trials leading to lack of uniformity in reporting outcomes amongst studies.

Evaluating the resolution of pain in men with PD is a laudable goal; any trial assessing pain must also contain a control group with comparable pain assessment, as resolution of pain is common in PD even without intervention.

It is also essential to consider penile deformities beyond curvature. Many men with Peyronie's disease report loss of length, loss of girth, indentation or hourglass-type deformities. It has also been proposed that Peyronie's disease may lead to a failure of the corporal veno-occlusive mechanism, and subsequent erectile dysfunction.

Changes in plaque dimension and morphology are poor study endpoints, not only because of the difficulty in reproducing plaque measurements, but also because the nature of the plaque itself has poor correlation to the actual clinical deformity.[7] Many studies include both men who present during the acute phase, as well as men with chronic, stable disease; these two groups of men are at very different points in their disease course and are likely to have different responses to any intervention. Mulhall et al have demonstrated that 33% of men screened with PD were not aware they had PD, suggesting that there is an unknown lag time in many

men between the onset of disease and their awareness of it. Therefore, the inclusion of men in clinical studies who have only recently noticed penile curvature, and assuming that they either have "new disease" or are in the acute phase of the disease, is suspect and fraught with methodological error.

There are gaps in patient representation in studies of non-surgical treatment for PD. A review of the foundational trials in medical management of Peyronie's disease revealed a lack of reporting of patient race/ethnicity, socioeconomic status, and sexual orientation. Accurate representation and reporting of patient demographics in clinical trials is essential for effective and equitable treatment in sexual medicine. This is of the utmost clinical relevance, as risk factors for PD such as diabetes, obesity, and smoking, which are prevalent amongst certain populations and in low-income neighborhoods, have been shown to be risk factors associated with PD.[9] Future studies should seek to address these issues in an effort to improve access of all PD patient populations to standard-of-care treatments.

2. Oral Medications

There is a lack of high quality, level one data to support any oral treatment regimens for PD. Each oral therapy reviewed in this update is associated with a scant number of studies supporting use and lacks formal FDA approval for the indication of Peyronie's disease (considered "off-label" use). Most of these studies are small, non-randomized, non-controlled case series without stringent inclusion criteria. Because there is no standard of care for PD, there is nothing precluding the utilization of placebo controls in well-designed trials, although enrolling patients who may be randomized to a placebo or sham arm in such a study has been historically difficult.

Clinicians should be wary of concluding that a treatment is effective simply on the basis of frequency of appearance within the literature, and in the absence of sound evidence derived from appropriate clinical trials. Finally, several agents have been proposed as rational treatments for PD based solely on their efficacy in animal models of PD, when there is concern that such models may not be representative of the human condition. **Current AUA Peyronie's Disease Guidelines recommend AGAINST offering oral therapy with Vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine due to a lack of demonstrated efficacy**[10]

A synopsis of published studies on oral pharmacotherapy for PD is presented in **Table 1**.

Table 1: Oral Medication Efficacy In Treatment Of Peyronie's Disease (Selected Studies)

Agent	Reference	N=	Study type	Change in Deformity
Vitamin E 200 mg tid	Pryor, et al.[11]	40	Randomized, placebo controlled crossover study	No improvement in penile curvature with Vitamin E.
Vitamin E	Gelbard, et al.[12]	97	Retrospective cohort questionnaire study	No improvement in penile curvature with Vitamin E.
Vitamin E 600 mg daily	Paulis, et al.[13]	70	Randomized controlled trial: vitamin E + intralesional verapamil, iontophoresis, blueberries and diclofenac versus same cocktail without vitamin E	12° improvement in curvature in Vitamin E group versus 7° in control group.
Colchicine 0.6 mg tid	Akkus, et al.[14]	24	Uncontrolled pilot study	Improvement in curvature in 37% of patients
Colchicine 1 mg bid	Kadioglu, et al.[15]	60	Retrospective cohort study	Improvement in curvature in 30% of patients, deterioration of curvature in 22%
Potassium aminobenzoate 3 g qid	Weidner, et al.[16]	103	Randomized, placebo controlled trial	No improvement in preexisting curvature with drug. Worsening curvature 3% with treatment versus 33% with placebo.
Pentoxifylline 400-800 mg tid	Smith, et al.[17]	71	Retrospective cohort study	69% of patients on pentoxifylline with sonographic improvement in calcifications versus 33% on vitamin E or no treatment.
Acetyl-l-carnitine 1 g bid	Biagotti, et al.[18]	48	Randomized controlled trial: Acetyl-l-carnitine versus tamoxifen	7° improvement in the acetyl-l-carnitine group versus 1° improvement with tamoxifen.
Propionyl-l-carnitine 2 g qd	Cavallini, et al.[19]	60	Randomized controlled trial: Propionyl-l-carnitine + intralesional verapamil versus tamoxifen +intralesional verapamil	12° improvement in the propionyl-l-carnitine group versus 2° improvement with tamoxifen.
Tadalafil 5 mg qd	Palmieri, et al.[20]	100	Randomized controlled trial: Tadalafil + shock wave therapy versus shock wave therapy alone.	No improvement in mean penile curvature or plaque size in either group.

Sildenafil 25 mg bid	Cocci, et al.[21]	50	Matched-Pair Comparison Analysis: Sildenafil + collagenase Clostridium hystoliticum versus collagenase Clostridium hystoliticum alone	26^{o} improvement in Sildenafil group versus 17^{o} improvement in collagenase Clostridium hystoliticum

2.1 Vitamin E

AUA Guideline Recommendation: Should not be offered (Evidence Strength Grade B).

Rationale: Vitamin E is an anti-oxidant that is thought to limit oxidative stress resulting from the generation of reactive oxygen species during the acute phase of wound healing.[22] Reduction in oxidative stress is purported to reduce collagen deposition within the tunica albuginea.

Outcomes: There are no reliable, randomized, double-blind placebo-controlled trials demonstrating improvement in penile deformity with vitamin E, with a number of studies demonstrating no improvement with use.[11,12]

2.2 Colchicine

AUA Guideline Recommendation: Insufficient evidence, more data is required.

Rationale: Colchicine inhibits fibrosis and collagen deposition by inhibiting neutrophil motility and activity, up-regulating collagenase activity, and reducing inflammatory mediators.[23]

Outcomes: There are no reliable, randomized, double-blind placebo-controlled trials demonstrating improvement in penile deformity with colchicine monotherapy. Uncontrolled trials have noted improvement in curvature in 30-36% of PD patients, and resolution of pain in 78-95% of men.[11,15] However, in the absence of placebo controls, these results are difficult to interpret.

Adverse Effects: The most common side-effects noted with colchicine include gastrointestinal distress and diarrhea (up to 26% of patients).[24] More severe side-effects, including rhabdomyolysis and agranulocytosis have been reported with therapeutic doses (less than 1% of patients).[25] CYP 3A4 inhibitors (indinavir, atazanavir, saquinavir, clarithromycin, ketoconazole, verapamil, grapefruit juice, among others) can lead to life threatening toxicity when taken concomitantly with colchicine, especially in the setting of hepatic or renal failure.

2.3 Potassium Aminobenzoate (POTABA®)

AUA Guideline Recommendation: Insufficient evidence, more data is required.

Rationale: POTABA® appears to have both anti-inflammatory and anti-fibrotic effects, stabilizing and decreasing tissue serotonin levels via increased monoamine oxidase activity, and inhibiting secretion of glycosaminoglycans from fibroblasts.[26] The net proposed effect is enhancement of endogenous tissue anti-fibrotic properties.

Outcomes: A single randomized, double-blind, placebo controlled trial has evaluated the utility of this agent in a population of 103 men with PD. Men receiving this medication (3g four times daily; 24 tabs per day) had no statistically significant changes in deformity compared to men receiving placebo, although plaque size was significantly reduced.[10] Worsening curvature was noted more frequently in the placebo group versus the treatment group (33% vs. 3%, p = 0.001).

Adverse Events: Adverse effect frequencies are poorly reported in the literature. The most common side-effects of POTABA® include anorexia, nausea, fever and rash, with gastrointestinal complaints serving as the primary reason for discontinuation of treatment.[27] Rarely, acute hepatitis has been reported.[28]

2.4 Pentoxifylline

AUA Guideline Recommendation: Insufficient evidence, more data is required.

Rationale: Pentoxifylline is a non-specific phosphodiesterase inhibitor, which acts to block transforming growth factor (TGF)-ß1 mediated inflammation, and prevents deposition of collagen type I.[29]

Outcomes: There are no reliable, randomized, double-blind placebo-controlled trials demonstrating improvement in penile deformity. A retrospective cohort study evaluated 71 men with sonographic evidence of penile calcifications, of whom 62 received pentoxifylline for one year, and 9 received vitamin E or no treatment. Improvement or stabilization of calcium burden was significantly more likely in the pentoxifylline group.[7] A prospective cohort study evaluated 46 men with PD who were treated with oral pentoxifylline and/or colchicine and penile traction therapy for six months.[30] There was a significant decrease in the degree of penile curvature and plaque size, there was a significant increase in peak systolic velocity, and there was a non-significant difference in end diastolic velocity, pulsatility index, and medication type of pentoxifylline or colchicine.

Adverse Effects: Side effects of pentoxifylline are generally mild, and noted in 1-2% of patients, and include nausea, dizziness and headache.[31]

2.5 Tamoxifen Citrate

AUA Guideline Recommendation: Should not be offered (Evidence Strength Grade C).

Rationale: Tamoxifen is a selective estrogen receptor modulator (SERM), which has been reported to reduce the release of TGF from fibroblasts, and ultimately reduce fibrogenesis.[29]

Outcomes: *Outcomes*: Data from a randomized, placebo controlled trial comparing tamoxifen to placebo in 25 patients with acute and chronic PD reported no difference in plaque area, penile curvature or improvement in pain between groups[32].

2.6 L-Carnitine

AUA Guideline Recommendation: Should not be offered as combination therapy with vitamin E (Evidence Strength Grade B). No specific statement about carnitine monotherapy.

Rationale: L-carnitine is a quaternary ammonium compound synthesized within the body. Its acyl esters (propionyl-l-carnitine and acetyl-l-carnitine) are believed to have antioxidant activity and have been used with varying success in diseases characterized by increased oxidative stress[33].

Outcomes: Acetyl-l-carnitine has been used in a randomized trial comparing it to tamoxifen in a population of 48 PD patients.[18] Patients receiving acetyl-l-carnitine were significantly more likely to have improvement of pain, and reduction of curvature (7 degree reduction). It should be noted that no true control group was used for comparison. A separate randomized trial of 60 PD patients comparing oral propionyl-l-carnitine plus intralesional verapamil to tamoxifen plus intralesional verapamil reported improved plaque size and curvature (average decrease of 12°) in the propionyl-l-carnitine arm[19].

Adverse Effects: Adverse effect frequencies when used for PD are not well reported in the literature. Rare side effects from L-carnitine include abdominal cramping, nausea, vomiting and diarrhea[34].

2.7 L-Arginine

AUA Guideline Recommendation: Insufficient evidence, more data is required.

Rationale: L-arginine is a conditionally essential amino acid. Its use has been investigated following basic science research demonstrating that L-arginine combined with phosphodiesterase inhibitors may prevent fibrosis in fibroblast cultures[35]. L-arginine stimulates nitric oxide synthase and, therefore, nitric oxide synthesis, and can inhibit collagen synthesis and induce fibroblast apoptosis.

Outcomes: The effect of L-arginine has not been studied in human clinical trials. L-arginine has purported efficacy in case reports, and as part of oral therapy protocols described in the literature; the efficacy of this treatment is questionable[36,37].

Adverse Effects: Adverse effects are rare and generally include gastrointestinal effects (nausea and vomiting), and headaches.[38]

2.8 PDE5 Inhibitors

AUA Guideline Recommendation: Not mentioned.

Rationale: PDE5 inhibitors, which block the degradation of cyclic guanosine monophosphate (cGMP) by phosphodiesterase, inhibit fibrosis through the effect of nitric oxide described above.[35] In addition, cGMP inhibits collagen synthesis and myofibroblast differentiation in cell cultures from PD plaques[39,40].

Outcomes: Tadalafil has been studied in a randomized, controlled trial of patients with PD and ED comparing shock wave therapy alone (50 patients) versus shock wave therapy plus tadalafil (50 patients), both for a total of 4 weeks in each arm[20]. Mean curvature and plaque size were unchanged in both groups at 12 weeks. Tadalafil use has additionally been studied in a retrospective review of 65 men with sonographically diagnosed non-palpable isolated penile septal scars, without evidence of penile deformity[41]. Among the 35 patients with this entity that were treated with tadalafil, sonographic resolution was noted in 69% versus 10% ($p < 0.05$) in those who were untreated. Sildenafil was studied in a matched-pair comparison analysis of 50 patients with PD, of whom 25 were treated with Sildenafil plus CCH (group A) and 25 were treated with CCH alone (group B)[3]. Mean penile curvature improved by 25.6° ± 9.1 in group A compared to 17.4° ± 6.6 in group B ($p < 0.01$). Mean IIEF-15 scores improved by 9.2 ± 5.4 in group A compared to 7.8 ± 12.7 in group B ($p < 0.01$).

Adverse Effects: The most commonly reported effects include headache, flushing, nasal congestion and heartburn, and temporary alteration in color vision (range 24-34% of patients).[42] Other side effects include myalgia, nausea, diarrhea, vomiting, and dizziness with risk of serious cardiovascular events in 0.2-0.5% of patients on sildenafil, vardenafil or tadalafil.

3. Topical Therapy

3.1 Verapamil

AUA Guideline Recommendation: Insufficient evidence, more data is required.

Rationale: Verapamil is a calcium channel antagonist that modulates calcium-dependent transport of extracellular matrix molecules. Verapamil can increase collagenase activity, modulate cytokine expression and inhibit fibroblast formation, all of which theoretically contribute to plaque regression.

Outcomes: In a study by Martin et al, topical verapamil failed to infiltrate the tunica albuginea.[43] Interestingly, in a later double-blinded study by Fitch et al, 18 men with PD were randomized to topical verapamil vs. placebo[44]. At 3 months, 61% reported a decrease in

penile curvature and 88% reported resolution of penile pain. Despite reported improvements in curvature, objective pre-treatment and post-treatment curvature measurement was not performed.

Adverse Effects: Most common side effects include varying degrees of skin irritation (8%).[44] First time users may experience mild itching/irritation. Very few patients report severe contact dermatitis, including pruritis, erythema, and edema (<1%).

3.2 Iontophoresis

AUA Guideline Recommendation: Should not be offered (Evidence Strength Grade C).

Rationale: Iontophoresis is the transdermal movement of topically applied medications, with the assistance of electrical current. It is also known as electromotive drug administration (EMDA).

Outcomes: A trial of 49 PD patients comparing verapamil plus dexamethasone vs. lidocaine (control) showed a significant decrease in plaque volume in the intervention group. However, penile deformity resolved in only 10% of the men, decreased in 75% of men, and remained unchanged in 15%.[46] Levine et al. performed a blinded, placebo controlled trial with 42 men with PD comparing transdermal verapamil to placebo (saline).[46] After objective pre- and post-treatment measurement of penile curvature with the assistance of intracavernosal papaverine and duplex doppler ultrasound, the authors found that 65% of men had modest deformity improvement in the verapamil group, compared to 58% of men in the saline group (p=not significant). It is unclear what the effect of the electrical current is on Peyronie's plaque.

In a 2013 study, Mehrsai et al. compared iontophoresis of verapamil plus dexamethasone vs. intralesional injection of verapamil plus dexamethasone.[47] During the 6-week therapy period, a single weekly dose of 10 mg verapamil and 4 mg dexamethasone solution was administered to 30 patients in each group either by EMDA or via conventional intralesional injection method. Pain with erection was reduced in the electromotive group, while there were no significant differences in penile deformity, plaque volume.[47] A 2018 study by Cavallini et al used hydroelectrophoresis to transdermally administer verapamil or hyaluronic acid in 61 men with Peyronie's disease.[48] 30 were treated with verapamil 10 mg (group 1) and 31 were treated with hyaluronic acid 8 mg (group 2). Pain, erectile function, plaque area, and penile deformity in both groups improved after treatment, but a notably higher improvement was observed in group 2.

4. Intralesional Therapy

Injectable Collagenase Clostridium Histolyticum (CCH is the only therapy approved by the FDA for management of Peyronie's Disease.[49] Alternative agents (ie corticosteroids, verapamil, interferon) have been reported and continue to be used by some practitioners however are used in an "off label" fashion and patients should be advised they are not FDA approved for this indication. It is recommended to perform a penile block before any penile injection for PD. Following dorsal penile block, a medium gauge needle (e.g. 25g) is used to repetitively puncture the plaque. At the same time, a small amount of the treating medication (usually diluted in 5-10 ml of normal saline) is injected into the plaque. Penile manipulation and sexual encounters should be avoided after injection; recommendations for duration of abstinence vary based on the agent used.[50] A synopsis of published studies on intralesional therapy for PD is presented in **Table 2**.

Table 2: Non-Oral Medical Treatments For Peyronie's Disease (Selected Studies)

Agent	Reference	N	Study Type	Change in Deformity
Iontophoresis: verapamil + dexamethasone (V+D) vs. lidocaine (L)	Di Stasi (2004)[29]	96	Randomized, placebo-controlled trial	Significant difference (43 → 21 degrees in V+ D group vs. no improvement in L Group)
	Levine (2007)[39]	42	Randomized, placebo-controlled trial	No difference
Intralesional Collagenase	Gelbard (1993)[41]	49	Randomized, placebo-controlled trial	Significant improvement with collagenase in men with curvature between 30-60°
	Gelbard (2013)[43]	417 415	Randomized, placebo-controlled trial	Mean decrease in curvature of 34% with collagenase vs 17% with placebo
Intralesional Verapamil	Rehman (1998)[40]	14	Randomized, placebo-controlled trial	No difference
	Levine (2002)[51]	140	Retrospective cohort	60% of patients had improvement
	Bennett (2007)[20]	96	Retrospective cohort	18% improved, 60% unchanged
Intralesional Interferon	Brake (2001)[52]	23	Prospective cohort	5% patients
	Hellstrom (2006)[36]	117	Multicenter, randomized, placebo controlled trial	Mean decrease in curvature of 27% with I vs. 9% with placebo)

4.1 Intralesional Collagenase Clostridium Histolyticum (CCH)

AUA Guideline Recommendations: May be offered in men with stable PD, curvature 30-90 degrees, and intact erectile function (Evidence Strength Grade B)

Rationale: Collagenase is an enzyme isolated from Clostridium histolyticum, which is capable of degrading tissue collagen.[53] This agent was approved for use in PD by the FDA in December 2013. The medication is injected side to side through the plaque at the point of maximum curvature in order to produce an effect like a “chemical knife”.

Outcomes: Two contemporary studies were essential in securing FDA approval for CCH. Both studies (n=417 and n=415) were a randomized-controlled evaluations of intralesional injection of CCH versus saline in patients with stable, chronic phase PD. Injection was combined with a post-injection program of penile molding/modeling. Analysis revealed that men treated with CCH and a program of penile modeling had a mean 34% (17 degrees) improvement in penile curvature, compared with a mean 18% (9 degrees) improvement in curvature amongst placebo treated men. 75% of men had at least a 25% improvement. Additionally, change in Peyronie’s Disease Questionnaire (PDQ) symptom bother score was significantly greater in men in the treatment group relative to control men (mean change of -2.8 versus -1.8, respectively, p=0.0037).

Collagenase injections are approved for the treatment dorsal or lateral plaques but not ventral plaques, due to potential risk of urethral injury. Plaque calcification has been shown to negatively predict collagenase treatment success.[54] One study found that when grouping calcification severity, no calcification had significant improvements in curvature when compared to moderate or severe calcification (28.1° vs 10.3°).

Recent data have highlighted a potential role for CCH in acute phase PD and in PD with ventral curvature. Nguyen et al. performed a multi-institutional analysis of retrospective data and found 918 men with PD, of which 134 (14.6%) were in the acute phase and 784 (85.4%) were in the stable phase.[55,56] Those in the acute phase group showed a mean curvature decrease of 13.5° degrees, compared to 15.6° in the stable phase (p=0.09). There was no statistically significant difference in adverse events. These findings were supported by a 2020 retrospective multi-center study of 134 acute phase patients and 784 stable phase patients. There was no significant difference in final change in curvature (13.5° vs 15.6°, P = .09), or frequency of treatment-related adverse events (11.9% vs 9.8%; P = .44).[54] Another 2020 study, from Cocci et al, assessed 74 patients in the acute phase who underwent a single CCH injection, and, at 3 mo showed improvement in curvature (19.3°) , PDQ-PS (- 2.7), PDQ-PP (- 1.2) and PDQ-BD (- 3.8).[57] Alom et al examined a case series of 228 patients who received collagenase, with 11% of patients having a ventral curve (83% dorsal, 50% lateral). The greatest relative improvement in curvature for this cohort was ventrally 49% (29.5°) when dorsal was 25% (15°).[58]

A 2019 study combined collagenase injections with a novel traction device showed a significant improvement of 49% (33.8°) vs the collagenase alone group of 31% (20.3 °).[59] There was also a difference in penile length gain +1.9 cm (+17%) in the combination group vs -0.7 cm (-4%) in the collagenase alone group. Another study from 2021 combined CCH with 4 hours of penile traction daily without a comparison group. The mean reduction of curvature was 23° (-41%).[60]

The importance of completing the full four cycles of CCH injections was emphasized in a 2021 study of 296 men which showed that 2/3 of men who fail to achieve 10 degrees or 20% curvature improvement with an initial 2 cycles achieved this with the final two cycles.[61]

Intralesional collagenase treatment is not a contraindication to subsequent surgical correction of residual penile plaque or deformity in patients with Peyronie’s Disease.[10] These findings were supported by a retrospective multi-center international study of 90 patients from 6 centers.[62] Two studies attempted to identify characteristics of patients who required subsequent surgery after CCH, highlighting baseline indentation, narrowing and hourglass deformity, as well as plaque calcifications and persistent curvature > 60 degrees as possible negative prognostic factors.[63,64]

Adverse Effects: Common events include injection site bruising/hematoma formation (35-70%). In the randomized trials above there were rare cases of penile fracture (corporal rupture, <1%). This may have been related to modeling, the treatment itself, or the resumption of sexual relations prior to the advised two-week hiatus (a four-week hiatus is now recommended). Recent evidence supports the conservative management of suspected fractures in men undergoing CCH.[54] Manufacturer video located at **https://peyronies-disease.xiaflex.com/hcp/resources/**.

4.2 Verapamil

AUA Guideline Recommendations: Clinicians may offer intralesional verapamil for the treatment of patients with Peyronie's disease. (Conditional Recommendation; Evidence Strength Grade C)

Rationale: Verapamil is a calcium-channel antagonist that modulates the calcium-dependent transport of extracellular matrix molecules, increases collagenase activity, modulates cytokine expression, and inhibits fibroblast formation.[51,52]

Outcomes: A 1994 study was the first intralesional verapamil study showing decreased curvature, plaque regression and improved erectile function.[66] In 1998, a randomized, placebo-controlled trial of only 14 men who underwent weekly injections of verapamil or placebo for 6 months was completed. Plaque volume decreased in 60% in the verapamil group versus 30% in the placebo group.

Erectile function improved in 40% of men in the verapamil group compared to none in the control group. Improvement in penile curvature was not statistically significant.[67] Published data consistently show beneficial effects of intralesional verapamil, with one recent study showing 100% of patients reporting pain resolution with 18% of patients experiencing a reduction in penile curvature and an additional 60% of patients showing stabilization of curvature.[68] Dell'Atti treated 59 patients with PD with either 1 injection of Verapamil 10 mg per week for a period of 12 weeks (group A, n=23), Tadalafil 5 mg once a day for a period of 3 months (group B, n=19), or both (group C, n=17).[69] All groups decreased in mean degree curvature but with non-significant differences between groups.

Adverse Effects: Common side effects are penile pain (10-15%), and ecchymosis (15-25%).[66,68]

4.3 Interferon

AUA Guideline Recommendations: Clinicians may administer intralesional interferon α-2b to patients with Peyronie's disease. (Moderate Recommendation; Evidence Strength Grade C)

Rationale: Interferons (INF) are cytokines that modulate the normal immune system to foreign antigens. In PD, interferons are thought to inhibit fibroblast proliferation, with subsequent decrease in collagen production. Additionally, interferon- -2b stimulates the activity of the enzyme collagenase.

Outcomes: In vitro studies have shown that INF-alpha2b and beta inhibit fibroblast and collagen production from fibroblasts derived from PD plaques.[70] Published data has shown mixed results,[71,72] but a recent multicenter, randomized, placebo-controlled trial of 117 men demonstrated a 30% reduction in penile deformity and 50% reduction in plaque size. However, no statistically significant improvement in penile pain or erectile function was found.[60] Stewart et al intralesionally injected interferon –α2b every 2 weeks for 6 to 24 treatments in 131 men with PD.[73] 110 patients presented with dorsal/lateral curvature (group 1) and 21 presented with ventral curvature (group 2). No significant difference was noted between the two groups in response rate, suggesting that interferon can be used for ventral curvature as well.

Adverse Effects: Flu-like symptoms such as fever, chills, and muscle aches (100%) may occur. Injection site reactions (pain/swelling/redness) (15-22%), headache (10%), tiredness (8%), diarrhea (<1%), loss of appetite, back pain, dizziness, dry mouth, taste changes, nausea, or vomiting may occur.[60]

5. Miscellaneous Therapies

5.1 Extracorporeal shock wave therapy (ESWT)

AUA Guideline Recommendations:

- Clinicians should not use extracorporeal shock wave therapy (ESWT) for the reduction of penile curvature or plaque size. (Moderate Recommendation; Evidence Strength Grade B)
- Clinicians may offer extracorporeal shock wave therapy (ESWT) to improve penile pain. (Conditional Recommendation; Evidence Strength Grade B)

Rationale: ESWT is a non-invasive treatment modality with 2 hypothesized mechanisms of action; direct damage to the plaque with subsequent remodeling and/or heat-induced increase in tunica vascularity resulting in an inflammatory reaction with up-regulated macrophage activity and resorption of calcification.[74]

Outcomes: Several studies have explored ESWT as a treatment for PD but have shown no definitive statistically significant improvement in penile curvature among men with stable phase curvature.[75]

One RCT evaluated 102 men randomized in 50:50 to ESWT or placebo,[76] and, in a sub-group analysis of 45 men with penile pain at baseline, showed improvement in pain visual analog scale scores of 17/20 (85%) men in the SWT group compared with 12/25 (48%) men in the placebo arm. (P=0.013, RR=0.29 (95% CI 0.09-0.087).

In 2019, Di Mauro et al studied 325 men with PD treated with ESWT and showed a significant improvement in plaque size, median erect penile length, median penile curvature, pain assessed by visual analog scale, each of the IIEF sub-domains, and all three PDQ domains.[77] 6 comparative studies including three randomized placebo-controlled trials found that SWT could reduce (OR 4.46, 95% CI 2.29–8.68, P < 0.0001) or eliminate pain (OR 5.86, 95% CI 2.66–12.92, P < 0.0001) and increase the percentage of men with lessening of penile plaques (OR 2.07, 95% confidence interval (CI) 1.11–3.85, P = 0.02).[78] There were, however, no statistically significant improvements in penile curvature and no overall improvements in erectile function. The clinical significance of plaque size as a study endpoint has been questioned.

Overall, studies testing treatment with ESWT for PD are extremely limited due to the heterogeneity of the devices and the settings used. According to AUA guidelines ESWT should not be used for the reduction of penile curvature or plaque size, but can be offered to improve penile pain.[9] Pain is typically a self-limited feature of PD and SWT is not widely accessible.

Adverse Effects: Penile ESWT is well tolerated. Reported side effects in a small percentage (6-8%) of patients include superficial,

self-limited bruising at the transducer site that did not require analgesia.[75-79]

5.2 Penile Traction

AUA Guideline Recommendation: Insufficient evidence, more data is required

Rationale: Application of continuous traction to fibrotic fascia has been shown to up-regulate collagenase activity with subsequent tissue remodeling. Traction therapy has been utilized with benefit in Dupuytren's contractures (DC) for more than 20 years.[80,81]

Since PD and DC are related disorders involving collagen deposition, chronic external traction of penile fibrotic tissue may theoretically yield benefit in PD. A synopsis of published studies on penile traction therapy (PTT) for PD is presented in **Table 3.**

Outcomes: While more high-level data is needed, recent studies support the probability that traction therapy results in a modest improvement in not only curvature, but also penile length. As length loss is a common complaint in PD, this may help affected patients as either a standalone or adjunctive treatment.

Table 3: Penile Traction Therapy (PTT) Efficacy In Treatment Of Peyronie's Disease (Selected Studies)

Reference	Study Type	Therapy	N	Daily PTT (hours)	PTT Duration (months)	Δ SPL (cm)	Mean Decrease in Curvature Magnitude %
Levine (2008)[82]	Single institution pilot study	FastSize Penile Extender	10	2-8	6	Increased 0.5-2	33%
Gontero (2009)[83]	Prospective phase II study	Andropenis	15	5-9	6	Average increase of 1.3	19%
Moncada (2018)[84]	Randomized controlled trial	PeniMaster PRO (PG)	41	3-8	3	PG group average increase of 1.8 from baseline (p<.05)	PG group 41% from baseline (p<.001)
		None	39	N/A			
Ziegelman (2019)[85]	Randomized controlled single-blind study	RestoreX® (RG)	63	0.5-1.5	3	RG group average increase of 1.5 vs 0 (p<.001)	18% decrease vs 4% increase (p<.01)
		None	27	N/A			
Alom (2019)[86]	Single institution prospective cohort	CCH	52	N/A	6	Average decrease of 0.7	31.2%
		CCH + other device	45	Average of 1.9		Average decrease of 0.4	30.2%
		CCH + RestoreX	16	Average of 0.9		Average increase of 1.75	49.4%

Adverse Effects: The most common complaints related to traction devices include difficulty keeping the device on the penis (50%) and penile discomfort (30%). A significant amount of patient motivation and compliance is required to adhere to recommended usage instructions. Innovations to traction technology designed for patient comfort and ease-of-use may result in ongoing improvements in compliance.[65] Skin injury and decreases in penile sensation or erectile function have not been reported.

5.3 Radiation Therapy

AUA Guideline Recommendation: Clinicians should not use radiotherapy (RT) to treat Peyronie's disease. (Moderate Recommendation; Evidence Strength Grade C).

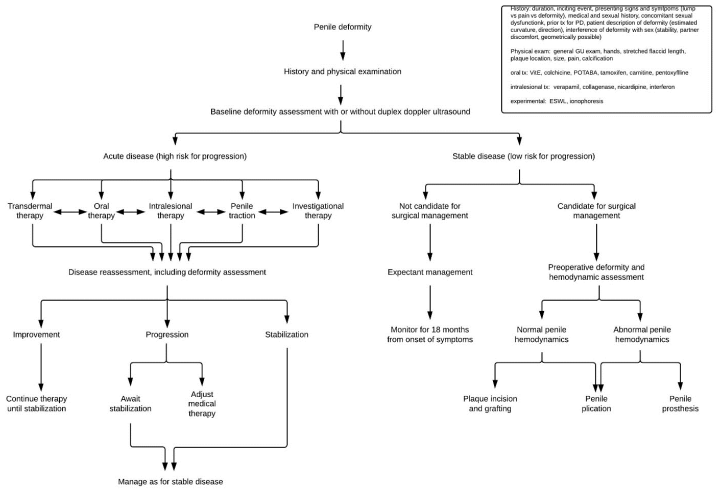

Figure 1: AUA guideline treatment algorithm

Radiation therapy (RT) is mainly of historical significance. There are no published randomized, placebo-controlled trials evaluating RT for PD. Results from a number of case series are difficult to interpret due to small numbers of patients, varied treatment protocols, and disparate methods for outcomes assessment.

5.4 Stem Cell Therapy

AUA Guideline Recommendation: Not mentioned

Stem cell therapy is designated for experimental use only

Rationale: Mesenchymal adipose-derived stem cells have been shown to mitigate fibrosis of the tunica albuginea in a rat model. It is known that mesenchymal stem cells (MSCs) may mitigate reactive oxygen species (ROS) and the release of profibrotic (TGF-β1), which is involved in the conversion of fibroblasts to myofibroblasts, a prominent histologic feature of Peyronie's disease.[67]

Outcomes: In a prospective study, 5 patients were enrolled and received injections of placental matrix derived (PM)-MSCs intracavernosally. First, 1 mL of PM-MSCs was diluted with 2 mL of isotonic saline solution, to a total of 3 mL. Up to 2 mL of the diluted PM-MSC solution was then injected in and around the Peyronie plaques. The rest of the PM-MSC solution was then injected evenly into both corpora at the base of the penis. Results showed statistically significant increases in peak systolic velocity occurred after PM-MSC injection ($P < 0.01$). Of a total of 10 plaques managed, 7 had disappeared completely at 3-month follow-up. Changes in end-diastolic velocity, stretched penile length, and penile girth were not statistically significant. The results of this study suggest that PM-MSCs may be beneficial and effective as a nonsurgical treatment in patients with PD, but findings are limited due to its small number of participants, lack of blinding, and absence of placebo control. Use of stem cells for PD is best reserved for a clinical trial setting in which patients are made fully aware of the uncertainties regarding this treatment modality.

6. Clinical Care Pathway for the Medical Management of Peyronie's Disease

The European Association of Urology has published a set of guidelines of penile curvature.[74]

The AUA has published a comprehensive guideline for the treatment and management of Peyronie's Disease.[10] **Figure 1** of the guideline is provided below.

Patients may be directed to the **Association of Peyronie's Disease Advocates**.

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