·Review·

Non-surgical therapy of Peyronie's disease

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Abstract

The present paper provides a review of the available non-surgical treatments for Peyronie's disease (PD). A review of published literature on oral, intralesional, external energy and iontophoresis therapies for PD was performed, and the published results of available treatment options reviewed. The authors' recommendations for appropriate non-surgical management of PD are provided. Although there are many published reports that show the efficacy of non-surgical therapies for PD, there is a lack of large scale, multicenter controlled clinical trials, which makes treatment recommendations difficult. Careful review of the literature does suggest that there are treatment options that make scientific sense and appear to stabilize the disease process, reduce deformity, and improve function. Offering no treatment at all will encourage our patients to pursue alternative treatments, which might do harm, and misses the opportunity to do some good. Clearly further work is necessary to develop safe and effective non-surgical treatments for PD. *(Asian J Androl 2008 January; 10: 79–87)*

Keywords: Peyronie's disease; penile induration; humans; injections intralesional; vitamin E; pentoxifylline; amino acids

1 Introduction

Peyronie's disease (PD) is a psychologically and physically devastating disorder that manifests as a fibrous inelastic scar of the tunica albuginea, causing penile deformity, penile curvature, hinging, narrowing, shortening, and painful erections. Despite multiple treatment options offered since Francois de la Peyronie described PD in 1743 [1], this disorder remains a considerable therapeutic dilemma to practicing physicians.

2 Mechanism

Contemporary thinking would considers PD as a disorder of wound healing, and as such it is similar to the formation of hypertrophic scars. Recent investigations have focused on the mechanisms of wound healing, fibrosis, scar formation as well as scar remodeling, and have correlated their findings to the Peyronie's population.

Study of the molecular etiology of PD has unearthed several important growth factors, which can be divided into profibrotic and antifibrotic groups. Profibrotic factors include TGF-1, which is an activator of collagen I synthesis [2], and which is released by neutrophils and macrophages during the acute and proliferative phases of wound healing. El Sakka *et al.* [3] found that in PD plaques, TGF-1 protein expression, as measured by Western blot, was overexpressed as compared to controls. In addition, TGF-2 and TGF-3 expression was not enhanced, suggesting that TGF-1 overexpression might play a role in PD development. Subsequently, TGF-1 was used to induce PD in a rat model, further solidifying its role as a central modulator of collagen deposition in PD [4].

A second group of profibrotic enzymes includes the fibrin/plasminogen activator inhibitor 1 (PAI-1) system. Plasmin breaks down the extracellular matrix both directly and indirectly by activating matrix metalloproteinases (MMP) to break down collagen. PAI-1 in turn inhibits MMP as well as plasminogen activator, which stimulates

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plasmin [5]. Fibrin itself has been recognized as an inducer of PD [6, 7], and has been used in causing PD in an animal model [8]. It has been documented that levels of TGF-1 and PAI-1 are increased in fibrin-induced PD plaques [7].

The major identified anti-fibrotic enzymes are the MMP. Although many different MMP have been identified, there are a few that appear more relevant in PD research. Collagen I breakdown is mediated by MMP 1 and 13, while for collagen III MMP 1, 3, 10 and 13 are most active. The only MMP produced by mammals that have been shown to substantially degrade Collagen 1 and III are types 1, 8 and 13 [9]. In addition, current studies are currently underway examining the possibility of fibrosis regression, through the induction of the nitric-oxide synthase (NOS) pathway.

Recent work has further elucidated the molecular biology of PD, and has unearthed potential targets for molecular-based therapies. Ryu *et al.* [10] evaluated the efficacy of a TGF-1 inhibitor in the treatment of induced PD in a rat model. The rats were injected with TGF-1 into the tunica albuginea, inducing a PD-like state. The rats were randomized into four groups: the control, PD group without treatment, PD with saline injections, and PD with IN-1130 injections. IN-1130 is a small molecule that inhibits activin receptor-like kinase 5 (ALK5), which is a receptor for TGF-1. The rats with PD that were treated with IN-1130 showed significant reduction in curvature and fibrosis when compared to those receiving either no injections or saline injections. The treatment group recorded post-treatment curvatures of 9.1° *vs.* 23.0° and 32.6° for the no injection and saline injection groups, respectively.

Del Carlo *et al.* [11] investigated the role of MMP and tissue inhibitors of matrix metalloproteinases (TIMP) in the pathogenesis of PD using harvested plaque from human PD patients. PD tissue samples were found to have reduced or absent levels of MMP 1, 8 and 13 when compared to patient-matched perilesional tunica. PD fibroblasts were then cultured with soluble MMP and TIMP after treatment with either TGF-1 or IL-1. They found that IL-1 stimulation increased the production of MMP 1, 2, 8, 9, 10 and 13 in PD fibroblasts, while TGF-1 increased the production of only MMP 10, and decreased the production of MMP-13, but markedly increased the production of all TIMP. These findings suggest that PD fibroblasts may be manipulated to encourage scar remodeling in the final phase of wound healing.

It is reasonable to consider that a genetic predisposition towards impaired wound healing and PD exists. Qian *et al.* [12] compared gene expression profiles in samples taken from PD tunica albuginea plaques, Dupuytren's contractures and normal palmar fascia, and found several gene family similarities between the PD and Dupuytren's

groups, including MMP-2, MMP-9, and thymosins TM10 and TM4 [12].

3 Non-surgical therapy for PD

Since the first description of PD in the published literature, clinicians have been searching for medical therapy options with few showing reliable results. Consistent success with medical therapies continues to evade the practicing urologist, although current research into the molecular pathophysiology of PD might one day lead to medical cure. Several nonsurgical options, however, are currently available which may stabilize or reduce deformity and improve sexual function. The evaluation of their efficacy has been compromised by small size of published clinical trials and most without any placebo control. Data outcomes are difficult to interpret without a validated questionnaire, and is complicated by the fact that there is a spontaneous improvement rate of 5%–12% [13–16]. The nonsurgical options for treatment of the pain and curvature of PD, including oral, topical, intralesional, external energy and combination therapies, are presented in the following subsections (Table 1).

3.1 Oral therapies

3.1.1 Vitamin E

Vitamin E was the first oral therapy described for the treatment of PD [17]. Vitamin E is a fat soluble vitamin that is metabolized in the liver, excreted in bile, and is postulated to have antioxidant properties in humans. Oxidative stress and the production of reactive oxygen species (ROS) is known to be increased during the acute and proliferative phases of wound healing, as it is neutrophils and macrophages that produce these ROS species [18], and the inflammatory phase of wound healing has been shown to be prolonged in Peyronie's patients [19]. Therefore, a biochemical mechanism does exist for Vitamin E use. Gelbard *et al.* [15] compared vitamin E therapy to the natural history of PD in 86 patients; no significant differences were found between the two groups in terms of curvature, pain, or the ability to have intercourse. In 1983, Pryor *et al.* [20] conducted a double-blind, placebo-controlled crossover study evaluating vitamin E for the treatment of PD in 40 patients. No significant improvements were noted in plaque size or penile curvature. The authors do not recommend vitamin E for the treatment of PD as there is no meaningful evidence of benefit in placebo-controlled trials.

3.1.2 Colchicine

Colchicine is an antigout agent that inhibits fibrosis and collagen deposition primarily by inhibiting neutrophil microtubules [21]. Colchicine has been used both as a

primary oral therapy for PD as well as in combination with other modalities. Akkus *et al.* [22] administered an escalating dose of colchicine in a non-randomized, non-placebo controlled fashion to 19 patients with PD over a 3–5-month period [22]. Of these patients, 36% noted a reduction in curvature, and 63% reported an improvement in the palpable plaque. Of the patients that were experiencing painful erections at the time of treatment initiation, 78% had resolution of this symptom. Kadioglu *et al.* [23] treated 60 patients with PD using 1 mg of colchicine twice daily, with a mean follow-up of 11 months [23]. They found significant improvement of pain in 95% of men; however, while 30% of patients reported improved curvature, 22% of patients reported worsened curvature. Safarinejad performed a randomized, placebo controlled trial of colchicine in 2004 with 84 men [24]. It was demonstrated that colchicine was no better than a placebo in improving pain, curvature angle, or plaque size as measured by ultrasound. Colchicine was not recommended by the authors due to its lack of demonstrated efficacy in placebo-controlled trials. The agent is also associated with gastrointestinal distress, including significant diarrhea, and rarely aplastic anemia.

3.1.3 Potassium aminobenzoate

Potassium aminobenzoate (Potaba, Glenwood) is a member of the vitamin B complex that is believed to increase the activity of monoamine oxidase in tissues, thereby decreasing local levels of serotonin and, therefore, possibly decreasing fibrogenesis. Potassium aminobenzoate is used for other medical conditions, including scleroderma, dermatomyositis and pemphigus. Zarafonatis and Horrax [25] first described the use of potassium aminobenzoate for the treatment of PD, and a subsequent European study published in 1978 reported a 57% improvement rate, with 9% complete resolution in a pooled cohort of 2 653 patients [26]. This study, however, had no control or placebo group. In 1999, Weidner *et al.* [27] published a randomized, placebo controlled trial of potassium aminobenzoate given 3 g orally four times per day for 1 year in 103 men. The only significant difference found between the two groups was plaque size, which in itself was not correlated with a decrease in penile curvature. A 2005 follow-up study also by Weidner *et al.* [28] suggested that the use of potassium amionobenzoate may protect against progression in PD plaques. Potassium aminobenzoate is expensive, and has low tolerability because of severe gastrointestinal side effects. It is also not recommended by the authors due to a lack of evidence regarding its efficacy in the treatment of PD.

3.1.4 Tamoxifen citrate

Tamoxifen is a nonsteroidal antiestrogen that acts by competing with estrogen binding sites in target tissues. In addition, tamoxifen affects the release of TGF from fibroblasts, and blocks TGF-receptors, thus potentially reducing fibrogenesis [29, 30]. In 1992, Ralph *et al.* [29] investigated tamoxifen in 36 patients with recent onset PD (duration less than 4 months) [29]. 80% of patients reported a reduction in pain, 35% noted a subjective reduction in curvature, and 34% reported a decrease in plaque size. A follow-up study in 1999 by Teloken *et al.* [31] failed to show any statistically significant difference between tamoxifen and a placebo, and there was an indidental report of alopecia in the active treatment group. We do not recommend the use of tamoxifen.

3.1.5 Carnitine

Carnitine is a naturally occurring metabolic intermediate. Carnitine facilitates the entry of long chain fatty acids into muscle mitochondria, which are then used as an energy substrate. Carnitine [32] is a hypothesized to inhibit acetyl coenzyme-A, which may help in the repair of damaged cells. Biagiotti and Cavallini examined the use of carnitine for PD in 2001. In their study, 48 men were divided into two groups to receive either tamoxifen at 20 mg twice daily for 3 months or acetyl-*L*-carnitine 1 g twice daily for 3 months. Overall, the men taking carnitine saw greater improvement in curvature, and had statistically significant improvement in pain. In addition, the patients taking carnitine reported far fewer side effects as compared to tamoxifen. At this time, more study is needed to elucidate the role of carnitine in the treatment of PD.

3.1.6 L-Arginine

L-Arginine is an amino acid that, when catalyzed by NOS, combines with oxygen to ultimately form nitric oxide (NO). It is known that inducible NOS (iNOS) is expressed in the fibrotic plaques of PD and suppression of iNOS exacerbates tissue fibrosis [33]. In 2003, Valente *et al.* [33] reported that *L*-arginine, given daily in the drinking water of a rat model with TGF-1 induced PD plaques caused an 80%–95% reduction in plaque size and in the collagen/fibroblast ratio [33]. In addition, *L*-arginine was found to be antifibrotic *in vitro*. This suggests that *L*-arginine, as a biochemical precursor of NO, might be effective in reducing PD plaque size. Further confirmatory human trials are needed before this agent can be recommended.

3.1.7 Pentoxifylline

Pentoxifylline is a nonspecific PDE inhibitor. Valente *et al.* [33] found that normal human and rat tunica albuginea, as well as PD plaque tissue, express PDE5A-3 and PDE4A, B and D. In their *in vitro* study, PD

Table 1. Nonsurgical therapies for Peyronie's disease (PD). ESWT, electroshock wave therapy.

Treatment	Mechanism of action	Comments
Oral		
Vitamin E	Antioxidant that theoretically reverses or stabilizes pathologic changes in the tunica albuginea.	Limited side effects, low cost. Efficacy not proven.
Colchicine	Inhibits fibrosis and collagen deposition.	Mixed reports of efficacy in non-controlled trials. Single randomized controlled trial failed to show benefit. Might cause gastrointestinal disturbances, including severe diarrhea.
Potassium aminobenzoate	Member of the vitamin B complex, thought to increase the activity of monoamine oxidase, thereby decreasing local serotonin levels, which might contribute to fibrogenesis.	Significant reduction in plaque size, but not curvature. Expensive, and difficult to tolerate due to gastrointestinal side effects.
Tamoxifen	Might reduce TGF-release from fibroblasts and might block TGF-β receptors, resulting in diminished fibrogenesis.	Efficacy not proven. Side effects might include alopecia.
Carnitine	Believed to inhibit acetyl coenzyme-A.	Efficacy not proven, and more investigation is needed.
L-Arginine	Amino acid substrate in the formation of nitric oxide, which is thought to be lacking in PD tissue.	Improvement in plaque size and collagen/fibroblast ratio in a rat model. Well tolerated.
Pentoxifylline	Nonspecific phosphodiesterase inhibitor that may reduce collagen levels in PD plaques.	Improvement in plaque size and collagen/fibroblast ratio in a rat model.
Topical		
Verapamil	Increases extracellular matrix collagenase secretion through fibroblast inhibition and decreases collagen and fibronectin synthesis and secretion. Decreases fibroblast proliferation	When administered topically the drug does not appear to penetrate into the tunica albuginea.
Intralesional		
Steroids	Anti-inflammatory and cause reduction in collagen synthesis.	Treatment with steroids is discouraged by the authors. Effects are unpredictable, and may cause atrophy and distortion of tissue planes.
Collagenase	Breakdown of collagen.	Statistically significant improvement in curvature has been noted in men with mild to moderate disease.
Verapamil	Same as topical verapamil.	Controlled and noncontrolled trials show promise as improvements in plaque volume, pain, and curvature have been reported.
Interferons	Decreased the rate of proliferation of fibroblasts in Peyronie's plaques *in vitro*, reduced production of extracellular collagen and increased production of collagenase.	Recent encouraging results with reports of improvement in curvature and pain. Dosing regimens and side effect profiles yet to be determined.
External energy		
Penile ESWT	ESWT-induced inflammatory response with resultant plaque lysis, improved vascularity, and the creation of contralateral scarring.	No statistically significant improvement noted in curvature, plaque size, or pain.
Electromotively administered	Effect of verapamil and steroids discussed previously. Electric current itself might have some beneficial	Objective improvements of plaque size and curvature have been noted. Adverse effects include erythema at

(To be continued)

Table 1 (continued). Nonsurgical therapies for Peyronie's disease (PD).   ESWT, electroshock wave therapy.

Treatment	Mechanism of action	Comments
verapamil with/without dexamethasone	effect on wound healing.	electrode site.
Combination therapy		
Vitamin E and Colchicine	Discussed previously. Synergistic effect possible.	Improvements in curvature and plaque size have been noted.
ESWT with intralesional verapamil injection	Discussed previously. Synergistic effect possible.	Significant improvement in plaque size compared with placebo.
Intralesional verapamil with oral carnitine or tamoxifen	Discussed previously. Synergistic effect possible.	Statistically significant subjective improvement in curvature, plaque size and erectile function in patients treated with carnitine and intralesional verapamil.
Penile traction devices		
fsPhysioMed penile extender	Expansion of contracted tissue might result in the formation of new connective tissue.	Early results demonstrate improvement in curvature, increase in length, and improvement in hinge effect. Side effects were limited to mild discomfort with the device.

fibroblasts were cultured with pentoxifylline and found to have increased cAMP levels and reduced collagen I levels as compared to controls. In addition, pentoxyfilline given orally to a TGF-1 induced PD rat model caused a decrease in PD plaque size and the collagen/fibroblast ratio. Brant *et al.* [34] reported a single case report of successful PD treatment using pentoxifylline alone [34]. Further studies are required to definitively examine pentoxifylline for the treatment of PD; however, its known biochemical effect and early animal-model success make it an attractive option for consideration.

3.2 Topical therapies
3.2.1 Verapamil
Interest in topical verapamil for the treatment of PD followed its success as an intra-lesional agent (see below). However, investigation has demonstrated that effective tunica albuginea tissue concentrations of verapamil are not achievable via topical application [35]. A recent three-arm trial without placebo demonstrated some benefit with topical verapamil [36], but this study was significantly compromised [37]. Therefore, the use of verapamil as a topical agent for PD is not recommended.

3.3 Intralesional therapies
3.3.1 Steroids

The powerful anti-inflammatory effect of steroids made them obvious agents for intralesional therapy of PD. In 1954, Bodner *et al.* [38] reported improvement in 17 patients treated with intralesional hydrocortisone and cortisone. In 1975, Winter and Khanna [39] showed no difference between patients treated with dexamethasone injections and the natural history of the disease. In 1980, Williams and Green [40] published a prospective study using intralesional triamcinolone. All patients were observed for 1 year after study enrollment; during that time only 3% of patients reported improvement. Triamcinolone was administered every 6 weeks for 36 weeks; 33% of patients reported subjective improvement, particularly in pain and plaque size. Currently, the use of intralesional steroids is discouraged because of the side effects of local tissue atrophy, fibrosis, immune suppression, and lack of objective measures of benefit.

3.3.2 Collagenase
Collagenase was first studied *in vitro* by Gelbard *et al.* in 1982 [41]. A subsequent clinical trial by that group demonstrated subjective improvement in 64% of patients within 4 weeks of treatment [42]. A decade after their initial study, they published their findings of a double blind trial in 49 men [43]. Statistically significant improvement in curvature was noted in the collagenase

treated group; however, maximal improvement ranged from 15° to 20° and was only seen in the patients with curvatures of less than 30° and plaques of less than 2 cm in length. Larger scale controlled trials of collagenase are currently underway.

3.3.3 Verapamil

Verapamil is a calcium channel blocker that has been shown in *in vitro* studies to inhibit local extracellular matrix production by fibroblasts, to reduce fibroblast proliferation, to increase local collagenase activity and to affect the cytokine milieu of fibroblasts [44, 45]. In 1994, Levine *et al.* [46] reported on 14 men who underwent a dose-escalation trial of biweekly intralesional injections of verapamil for 6 months. Significant improvement in plaque associated narrowing was noted in all patients, and curvature was improved in 42%. The first randomized single-blind trial of intralesional verapamil was published in 1998 [47]. Significant improvement were noted in terms of erection quality and plaque volume. A non-statistical trend towards improvement in curvature was also noted. As a follow-up, Levine and Estrada [48] reported on 156 men enrolled in a prospective non-randomized trial of PD men with a mean follow-up of 30.4 months. A local penile block was performed with 10–20 mL 0.5% bupivicaine, followed by injection of 10 mg verapamil diluted in 6 mL sterile normal saline (total volume 10 mL) into the Peyronie's plaque using 1–5 skin punctures, but with multiple passes through the plaque. The goal is to leave the drug in the needle tracks, not to tear or disrupt the plaque. Injections were administered every 2 weeks for a total of 12 injections. Of patients with pain, 84% achieved complete resolution, 62% were found on objective measurement to have improved curvature ranging from 5–75° (mean 30°), and only 8% of patients had measured worsening of curvature. More recently, Bennett *et al.* [49] administered six intralesional injections (10 mg in 5 mL) every 2 weeks to 94 consecutive patients with PD [49]. Follow-up was at 5.2 months after completion of the 6th injection. Of patients, 18% ($n = 17$) were found to have improved curvatures (average improvement 12°), 60% ($n = 56$) had stable curvature, and 22% ($n = 21$) had increased curvature (average increase 22°). All patients with pretreatment penile pain had improvement at follow-up. The authors suggest that these data support intralesional verapamil for the stabilization of PD. It might be that six injections provides stabilization but is insufficient to accomplish reduction of curvature. Currently, we recommend a trial of six injections with each injection occurring every 2 weeks. If no improvement is noted by the patient, the therapy may be terminated, the verapamil dose can be increased to 20 mg, or interferon (IFN) injections may be offered. We consider verapamil contraindicated in patients with ventral plaques or extensive plaque calcification.

3.3.4 IFN

Duncan *et al.* [50] reported in 1991 that IFNs decrease the rate of proliferation of fibroblasts in Peyronie's plaques *in vitro*, reduce the production of extracellular collagen, and increase the activity of collagenase. Initial studies performed by Wegner *et al.* [51, 52] demonstrated low rates of improvement, but a high incidence of side effects, including myalgias and fever. In 1999, Ahuja *et al.* [53] reported on 20 men who received 1×10^6 units of IFN-α-2b biweekly for 6 months. Of these patients, 100% reported softening of plaque, 90% of men presenting with pain had improvement, and 55% had a subjective reduction in plaque size. Dang *et al.* [54] administered 2×10^6 units to 21 men biweekly for 6 weeks, and found objective curvature improvements in 67%, and improvement in pain in 80%. Seventy-one percent of patients reported improvement in ED symptoms. In 2006, Hellstrom *et al.* [55] reported on a placebo controlled, multicenter trial of 117 patients who underwent biweekly injections of 5×10^6 units for a total of 12 weeks. Average curvature in the treatment group improved 13°, versus 4° in the placebo arm, and 27% of patients in the treatment group had measured improvement versus 9% of the saline group. Pain resolution was noted in 67% of the treatment patients versus 28% for the placebo. IFN therapy requires investigation to further define efficacy, dosing regimens, and side effect profiles.

3.4 External energy therapies

3.4.1 Penile electroshock wave therapy (ESWT)

Local penile ESWT has been suggested to be of benefit for the treatment of PD. Various hypotheses about its mechanism of action exist, including direct damage to the plaque resulting in an inflammatory reaction with increased macrophage reaction leading to plaque lysis, improved vascularity resulting in plaque resorption, and the creation of contralateral scarring of the penis resulting in "false" straightening [56]. Hauck *et al.* [57] randomized 43 men to ESWT or oral placebo for 6 months [57]. No significant effect was noted in terms of curvature, plaque size, or subjective improvement in sexual function or rigidity. More recent work from a German group randomized 102 men to ESWT or to receive placebo shocks [58, 59]. There was no statistically significant difference found between the groups for plaque size, improvement of deformity, or sexual function posttreatment. ESWT is currently not recommended as therapy for PD.

3.4.2 Iontophoresis

Iontophoresis involves the transport of ions through

tissue by means of an electric current. Several studies have investigated the efficacy of topically applied verapamil with or without dexamethasone with enhanced penetration using iontophoresis [60–63]. In 2002, Levine *et al.* [64] confirmed that verapamil was found within the exposed tunica albuginea by examining surgically re-trieved tunica albuginea from patients after a single intra-operative exposure during plaque incision and grafting surgery. Di Stasi *et al.* [63] recently reported on a prospective, randomized study of 96 patients treated with 5 mg verapamil plus 8 mg dexamethasone using ionto-phoresis versus 2% lidocaine delivered electromotively. Of patients in the verapamil/dexamethasone group, 43% noted objective improvement in plaque size and curvature; no changes were noted in the lidocaine group. In 2005, Greenfield *et al.* [65] reported on the use of 10 mg verapamil versus saline iontophoresis. Patients were as-sessed using papavarine-induced erections prior to and 1 month after treatment. Of patients in the verapamil group, 65% demonstrated improvement in curvature, versus 58% in the saline group. Mean curvature im-provement was 9.1° in the treatment group versus 7.6° in the saline group, which is not as robust as intralesional verapamil injections. The authors suggested that the elec-tric current itself might have some beneficial effect on wound healing, which is known and supported in the dermatologic literature [66]. Further investigation into iontophoresis is needed.

3.5 Combination therapy
3.5.1 Vitamin E and colchicine
A placebo controlled study by Preito Castro *et al.* [67] randomized 45 patients to receive vitamin E and colchicine or ibuprofen. Statistically significant improve-ments in curvature and plaque size were noted in the group treated with vitamin E and colchicine as compared to the group receiving ibuprofen. Patients in the vitamin E and colchicine arm reported a greater decrease in pain, although this did not reach statistical significance.

3.5.2 ESWT with per perilesional verapamil injection
In 1999, Mirone *et al.* [68] prospectively examined two groups of PD patients; one group was treated with ESWT, while the other received ESWT and perilesional verapamil injections. A 52% improvement in plaque size by ultrasound was noted in the ESWT-only group com-pared to 19% for the combination therapy. A follow-up study by the same investigators involving 481 patients demonstrated a 49% improvement in plaque size among those treated with combination therapy [69].

3.5.3 Intralesional verapamil with oral carnitine or tamoxifen
In 2002, Cavallini *et al.* [70] randomized 60 men to receive intralesional verapamil plus oral carnitine or intralesional verapamil plus oral tamoxifen. Statistically significant subjective improvements in curvature, plaque size and erectile function were found in the carnitine group. No difference in improvement of pain was noted between the two groups.

3.6 Penile traction devices
The use of tissue expanders has long been a main-stay of treatment in the orthopedic, oral-maxillofacial and plastic surgical fields. It is well-documented that gradual expansion of tissue results in the formation of new bone and connective tissue. Initial work has been done to evaluate the efficacy of a penile extender device (fsPhysioMed; FastSize LLC, Aliso Viejo, CA, USA)) for the treatment of PD. A pilot study at our institution of 10 patients found that daily application of the fsPhysioMed device for 2–8 h per day for 6 months resulted in a 33% measured improvement in curvature (ranging from a 10° to 45° improvement and resulting in an improvement in average curvature from 51° to 34°), an increase in flac-cid stretched penile length ranging from 0.5–2.0 cm, and an improvement in hinge effect in all those with advanced narrowing or indentation. No patients noted recurrence or worsening of curvature during 6 months of follow-up, and there was no incidence of local skin changes, ulceration, loss of sensation, or worsening of curvature. Long term and larger studies are indicated.

4   Conclusion

Our current practice favors a multi-modal approach for non-surgical therapy for PD. All patients are pre-scribed 400 mg pentoxifylline orally three times a day, with *L*-Arginine 1 000 mg twice a day. Patients are en-couraged to use the fsPhysioMed device 2–8 h per day for 6 months, and are offered intralesional verapamil in-jections as a means to improve curvature and, if present, pain. As a result of increased interest in this disorder as well as more sophisticated basic science and clinical research, effective and reliable non-surgical treatments will hopefully emerge. In the meantime, there are a num-ber of non-surgical treatment options that offer some benefit with respect to disease stabilization as well as reduction of deformity and improved sexual function.

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