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**Systematic review of the non surgical management of Peyronie's disease**

Verze P *et al*. Peyronie’s disease: Medical treatment

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**Abstract**

This systematic review shows the “Status quo” on medical treatment for Peyronie's disease (PD). PD is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity. The aetiology of PD is unknown. Nowadays the most widely accepted hypothesis proposed by Gonzalez-Cadavid *et al*, is repetitive microvascular injury or trauma to the tunica albuginea. Physicians have proposed several medical alternatives for treatment of this disease with few effective results. Nevertheless, as of today nonsurgical options are currently available, and some of them are able to stabilize or even reduce deformity while improving pain relief and sexual function. A systematic literature search throughout the Medline database was carried out. The controlled vocabulary of the medical subject headings (MeSH) database employs the specific term “penile induratio” for PD. A total of 50 articles on PD were found. Studies were selected based on clinical relevance. The recommended standard of care for PD involves an initial treatment in the acute phase. Several non-operative treatment options have been used. Unfortunately no further substantial, quality evidence on the use of medical therapy currently exits. There is, however, an increasingly enhanced interest in this disorder and basic scientific and clinical research will eventually lead to a more effective methodology to study the disease.

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**Key words:** Peyronie’s disease; Non surgical; Dupuytren; ESWT

**Core tip:** Ince the first medical publication on Peyronie’s Disease, physicians have proposed several medical alternatives for treatment of this disease. As of today nonsurgical options are currently available. A consistent number of non-surgical treatment options that offer some benefit with respect to disease stabilization, alleviation, as well as reduction of deformity and improved sexual function are available including oral treatment with potassium para-aminobenzoate, intralesional treatment with interferon, iontophoresis with verapamil 5 mg and dexamethasone 8 mg and extracorporeal shock-wave treatment.

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**INTRODUCTION**

Peyronie’s disease (PD) is a connective tissue disorder, characterised by the formation of a fibrotic lesion or plaque in the tunica albuginea, which leads to penile deformity[1]. The true prevalence of PD is unknown. An evaluation of existing epidemiological data on PD revealed a prevalence rate of 3.2%. However the actual prevalence of PD may be even higher, considering many patients' reluctance to report this embarrassing condition to their physicians. The latest version of the EAU guidelines[1] reports a prevalence rate of 0.4%–9%.

The aetiology of PD is unknown. Nowadays the most widely accepted hypothesis proposed by Gonzalez-Cadavid *et al*[2], is repetitive microvascular injury or trauma to the tunica albuginea. PD starts with an acute inflammatory process. The progression of inflammation causes a proliferation of the tunical fibroblasts, some of which differentiate into myofibroblasts with a disproportionate production of collagen, the persistence of fibrin, and resulting elastin fragmentation. This prolonged inflammatory reaction generates the remodelling of connective tissue into a dense fibrotic plaque. As a result of Penile plaque the penis develops a curvature which, in the case of severe bending, can prevent vaginal intercourse. Comorbidities and risk factors associated with the disease are diabetes, hypertension, lipid abnormalities, ischaemic cardiopathy, erectile dysfunction, smoking, and excessive consumption of alcohol[3]. An accompaniment with Dupuytren contracture is reported in 9%-39% of PD patients. Men experiencing sexual dysfunction after Radical Prostatectomy have a higher PD incidence rate then the general population and therefore should be routinely evaluated for PD. Younger men and Caucasian men are at increased risk for PD[4]. The natural course of PD indicates that penile curvature stabilizes in 47%-67% of patients or worsens in 30%-50% of patients. As well, spontaneous improvement is reported in only 3%-13% of patients[5]. In later phases, once the plaque becomes calcified the possibilities that penile curvature can be corrected are not as likely as in the early stage of the disease.  Thirty-five percent to forty-five percent of patients can experience referred pain at early stages of the disease. However in 90% of men the pain tends to abate with time, usually during the first 12 mo after onset.

Nelson *et al*[6] reported that, besides the physiologic and functional alteration of the penis, 48% of men with PD experience mild-to-moderate depression as revealed through validated mental health questionnaires.

Since the first medical publication on PD, physicians have proposed several medical alternatives for treatment of this disease with few effective results. The most recent findings on the molecular pathophysiology of PD, though not conclusive, nonetheless give a bigger picture of the mechanisms underlying the evolution of the plaque formation and may one day guide to medical treatment. Nevertheless, as of today nonsurgical options are currently available, and some of them are able to stabilize or even reduce deformity while improving pain relief and sexual function. Unfortunately the studies found in literature, though providing evidence of the efficacy of these options, are compromised by the small size of the sample or the absence of a placebo control. Moreover, PD assessment lacks a validated questionnaire that allows for the interpretation of the data outcomes, and the analysis of the data is complicated by the fact that the spontaneous improvement rates reported are 5%-12%[7–10].

In light of existing Nonsurgical options for PD pain treatment and curvature including oral, intralesional, topical, and combination therapies, the aim of the current paper is to investigate, through a systematic review, the currently available Medical approaches for treating PD.

**METHODOLOGY**

A systematic literature search throughout the Medline database was carried out. The controlled vocabulary of the medical subject headings (MeSH) database employs the specific term “penile induratio” for PD. In order to identify relevant articles, the search included the MeSH terms, penis abnormalities, male, penile curvature and the terms “Peyronie’s Disease” and “Induratio Penis Plastica”. A total of 50 articles on PD were found. Relevant English-language articles were abstracted and reviewed using the reference list to identify additional potential articles for review. Studies were selected based on clinical relevance. If more than one article was published in the same study population, the study with the larger sample size was selected.

**NON SURGICAL TREATMENT**

The recommended standard of care for PD involves an initial treatment in the acute phase (first year) of this condition when symptoms are present and the plaque is not yet densely fibrotic or calcified[9]. Several non-operative treatment options have been used. Up to the present the EMA (European Medical Association) has not approved any medication for the treatment of PD with the except of potassium para-aminobenzoate (Potaba) which has been classified as ‘‘possibly effective’’ for PD by the US Food and Drug Administration.

The studies collected for this review showed contradictory results on conservative treatment for PD making it difficult to provide recommendations in an everyday real-life setting.

**ORAL TREATMENT**

***Vitamin E***

 Vitamin E (tocopherol) is a fat-soluble compound that acts as a natural antioxidant to reduce the number of oxygen-free radicals produced in the energy metabolism. It has also been shown to play a role in DNA repair and in immune modulation[11]. The widely accepted use of tocopherol in the treatment of PD attests to the hypothesis that it inhibits fibrosis by acting as a scavenger of oxygen free radicals. *In vitro* studies examining the effect of free radicals on human cavernosal cells have shown a direct association with increased collagen production[12]. Based upon these findings it is logical to conclude that inhibition of free radicals (*i.e.*, with use of tocopherol) should decrease the rate and degree of fibrosis. However, *in vivo* data has failed to reveal any concrete benefits in PD patients [13,14]. To date, tocopherol is commonly prescribed by most urologists in once- or twice-daily doses of 400 IU because of its wide availability, low cost, and safety. In 1983, Pryor *et al*[10] 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 therefore did not recommend vitamin E for the treatment of PD as there was no meaningful evidence of its benefit in placebo-controlled trials.

***Potassium para-aminobenzoate (Potaba)***

Potassium paraaminobenzoate (Potaba, Glenwood) is a vitamin B complex and is believed to exert an antifibrotic effect through an increase in oxygen uptake by the tissues, a rise in the secretion of glycosaminoglycans, and enhancement of the monoamine oxidases activity in tissues thereby decreasing local levels of serotonin and, in turn, possibly decreasing fibrogenesis. A prospective double-blinded controlled study by Shah *et al*[15] analyzed 41 patients with PD and showed that, while penile pain was significantly improved by potassium para-aminobenzoate (12 g/d for 12 mo) neither penile curvature nor penile plaque size were affected. Weidner *et al*[16], in a prospective randomised double-blind placebo-controlled trial evaluating 103 patients with PD, found that potassium para-aminobenzoate (3 g/d four times daily for 12 mo) decreased penile plaque size significantly but had no effect on penile curvature or penile pain. The Treatment-emergent adverse events reported were: nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion, and difficulty concentrating and therefore no serious adverse events have been reported.

***Tamoxifen***

Tamoxifen is a nonsteroidal oestrogen receptor antagonist. The action mechanism which should determines changes in PD is the modulation of the transforming growth factor (TGF)b1 secretion by fibroblasts. Teloken *et al*[17] published a placebo controlled randomised study performed in 25 patients in the late stages of PD with a mean disease duration of 20 mo. The results of this study showed that Tamoxifen 20 mg twice daily for 3 mo failed to demonstrate significant improvement in pain, curvature, or plaque size[17].

***Colchicine***

Colchicine is a medication that is commonly employed in the treatment of acute attacks of gout. Its anti-inflammatory effects suggested its possible use in treating PD. Kadioglu *et al*[18] reported on the results of a study on 24 men, half of whom were given colchicines (0.6-1.2 mg daily for 3-5 mo) and whose painful erections and penile curvature were shown to improve in 50% of them with penile plaque decreasing or disappearing completely. Akkus *et al*[19] presented the results of a study involving 60 men treated with colchicine 0.5-1 mg daily for 3-5 mo and subsequently increased to 2 mg twice daily. Following this treatment penile pain was resolved in 95% of the cases while penile curvature improved in 30%. The reported treatment-emergent adverse events from the use of colchicine were gastrointestinal effects (nausea, vomiting, diarrhea), which were improved by dose escalation.

Finally, Prieto Castro *et al*[20] investigated the combination of vitamin E and colchicine (600 mg/d and 1 mg every 12 h, respectively) in patients with early-stage PD for 6 mo. The results of this study showed a significant improvement in plaque size and curvature, but not in pain when compared with ibuprofen 400 mg/d for 6 mo.

***Acetyl esters of carnitine***

It has been suggested that carnitine can reduce intracellular calcium levels in endothelial cells which, in turn, may eventually suppress fibroblast proliferation and collagen production thereby reducing penile fibrosis. To date, only 1 randomised double-blind study evaluating the efficacy of acetyl-L-carnitine has been conducted by Biagiotti and Cavallini[21]. In 48 patients with early-stage PD, subjects were given either tamoxifen 20 mg twice daily or acetyl-L-carnitine 1 g twice daily for 3 mo. After 3 mo, acetyl-Lcarnitine was significantly more effective than tamoxifen in reducing pain and curvature and in inhibiting disease progression, but not in reducing penile plaque size (both tamoxifen and carnitine significantly reduced plaque size.

Another study investigated the combination of propionyl-l-carnitine (2 g/d for 3 mo) with intralesional verapamil (10 mg weekly for 10 wk). The results showed that this combination therapy significantly reduced penile curvature, plaque size, and disease progression when compared with intralesional verapamil combined with tamoxifen (40 mg/d) for 3 mo [22].

***Pentoxifylline***

Pentoxifylline is a nonspecific phosphodiesterase inhibitor that downregulates TGFb1 and increases fibrinolytic activity. Valente *et al*[23] found that normal human and rat tunica albuginea as well as PD plaque tissue expresses PDE5A-3 and PDE4A, B and D. In their in vitro study, PD fibroblasts were cultured with pentoxifylline and found to have increased cAMP levels and reduced collagen I levels as compared to controls. An increase of nitric oxide levels may be effective in preventing the progression of PD or reversing fibrosis. Brant *et al*[24] performed a study on 62 patients with PD, and showed that treatment with pentoxifylline for 6 mo appeared to stabilize or reduce calcium content in penile plaques and also tended to improve penile curvature.

***Phosphodiesterase type 5 inhibitors***

The rationale for the use of a phosphodiesterase type 5 (PDE5-I) in PD comes from animal studies which show that PDE5-l can reduce the collagen/smooth muscle and collagen III/I ratios and increase the apoptotic index in PD like plaque[25]. In a recent retrospective controlled study Chung *et al*[26] investigated the role of daily tadalafil (2.5 mg for 6 mo) which resulted in a statistically significant (*P* < 0.05) resolution of the septal scar in 69% of patients compared with 10% in the control group (no treatment). However, this study included patients with isolated septal scars without evidence of penile deformity[26].

**INTRALESIONAL TREATMENT**

The injection of a medication directly into the penile plaque results in restricted delivery and higher drug concentrations inside the plaque.

***Steroids***

The powerful anti-inflammatory effect of steroids makes them obvious agents for intralesional therapy of PD. Steroids operate by counteracting the inflammation responsible for Peyronie’s plaque progression via inhibition of phospholipase A2 and suppression of the immune response and by diminishing collagen synthesis. In 1954, Bodner *et al*[27] reported improvement in 17 patients treated with intralesional hydrocortisone and cortisone. In 1975, Winter and Khanna[28] showed no difference between patients treated with dexamethasone injections and the natural history of the disease. Cipollone *et al*[29], in a single-blind placebo-controlled study with intralesional administration of betamethasone, reported that no statistically significant changes were seen in penile deformity, penile plaque size, nor penile pain during erection. Adverse effects included tissue atrophy, thinning of the skin, and immune suppression.

***Verapamil***

Verapamil is a calcium channel antagonist that is thought to selectively inhibit calcium ion flux in both cardiac muscle and cells responsible for intracardiac conduction, as well as in coronary and systemic arteries. The rationale for its use in the intralesional treatment of patients with PD is based on in-vitro data that demonstrates transport of extracellular matrix molecules that include collagen, fibronectin, and GAGs as a calcium-dependent process[30]. A concomitant increase in collagenase activity, modification of the inflammatory response in the early phase of the disorder, and inhibition of fibroblast proliferation in the plaques are other proposed mechanisms. Shirazi *et al*[31] reported in a randomized placebo-controlled study that no statistically significant differences in plaque size, penile curvature, penile pain during erection, and plaque ‘‘softening’’ were seen.

***Clostridial collagenase***

Clostridial collagenase is a chromatographically purified bacterial enzyme that selectively attacks collagen and is known to be the primary component of the PD plaque. Collagenase was first studied *in vitro* by Gelbard *et al*[32] in 1982. A subsequent clinical trial by that group demonstrated subjective improvement in 64% of patients within 4 wk of treatment[33]. A decade after their initial study, the group published their findings of a double blind trial in 49 men[34]. In this study which compared the effects on plaque size and penile deformity of intralesional purified clostridial collagenase (6000–14.000 U) and saline placebo, the overall response was 36% with clostridial collagenase compared with 4% with placebo (*P* < 0.007). Follow-up was only 3 mo. Response rates were even higher in patients with smaller plaques and curvature < 60°. The efficacy of intralesional collagenase injections (three injections of clostridial collagenase, 10000 U/0.25 cm3 per injection, administered over 7-10 d and subsequently administered over 7-10 d at 3 mo) was assessed over a non-placebo-controlled short-term follow up study in a small population of men with PD[35]. This study showed a significant reduction from baseline in the deviation angle, plaque thickness, and plaque extension, but it was biased by an incorrect scientific approach. The most commonly reported side effects were penile pain, contusions, and ecchymosis.

***Interferon***

Duncan *et al*[36] 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 improve the activity of collagenase. Hellstrom *et al*[37], demonstrated that intralesional injections (5 × 106 units of interferon a-2b in 10 ml saline two times per week for 12 wk) improved average curvature in the treatment group by 13°, *vs* 4° in the placebo arm, and that 27% of patients in the treatment group had measurable improvement *vs* 9% of the saline group. Pain resolution was noted in 67% of the treatment patients *vs* 28% for the placebo[37]. Side effects include myalgias, arthralgia, sinusitis, fever, and flulike symptoms which can be effectively treated with nonsteroidal anti-inflammatory drugs before interferon injection.

**TOPICAL TREATMENTS**

***Topical verapamil***

Fitch 3rd *et al*[38] presented the results of a small randomised placebo controlled study on topical verapamil applied as gel 15% to the penile shaft twice daily. The penile curvature, plaque size, and penile pain were significantly improved. After 9 mo of treatment better improvement was reported compared with the results at 3 mo, demonstrating that a prolonged treatment period may be important. However, a lack of evidence exists supporting that topical verapamil applied to the penile shaft produces adequate levels of active compound within the tunica albuginea.

***Iontophoresis***

To overcome limitations of topical therapies, emphasis has more recently been placed on testing modalities such as iontophoresis, which enhances the local uptake of drugs. Iontophoresis involves the application of an external electric force to induce further (electromotive) penetration of topical medication. Di Stasi *et al*[39] presented their results of a randomised double blind controlled study, demonstrating that iontophoresis with verapamil 5 mg and dexamethasone 8 mg resulted in a statistically significant improvement in penile curvature and plaque size. On the other hand, Greenfield *et al*[40] with a randomized double-blind placebo controlled study showed that penile curvature was not statistically improved after iontophoresis with verapamil 10 mg. No significant events with Iontophoresis were reported.

***Extracorporeal shock wave lithotripsy***

The mechanism of action involved in extracorporeal shock wave lithotripsy (ESWL) for PD is still unclear, but there are two hypotheses. In the first hypothesis, ESWL may work by directly damaging and remodeling the penile plaque. In the second hypothesis, ESWL may increase the vascularity of the area by generating heat, resulting in an inflammatory reaction with increased macrophage activity causing plaque lysis and eventually leading to plaque reduction. Hauck *et al*[41] in an exploratory meta-analysis detected that ESWT seems to have an effect on penile pain during erection and on the improvement of sexual function. Pain seems to resolve faster after ESWT than during the course of the natural history. The effect on plaque size and penile curvature is less impressive. This result were confirmed by Palmieri *et al*[42] that published the only existing prospective randomised double-blind placebo-controlled study where they investigated four weekly treatment sessions of ESWL, with each session consisting of 2000 focused shock waves which resulted in significant improvement for penile pain only.

***Traction devices***

The use of tissue expanders has long been a mainstay of treatment in the orthopedic, oral-maxillofacial and plastic surgical fields. A continuous traction in Dupuytren contracture increases the activity of degradative enzymes. This first leads to a loss of tensile strength and subsequently to solubilization. This is followed by an increase in newly synthesized collagen. Levine *et al*[43], in an uncontrolled study, applied this technique on 10 patients with PD whereby application of the the FastSize Penis Extender was the only treatment for 2-8 h/d for 6 mo. Penile curvature was reduced in all men from 10° to 45°, with an average reduction of 33% (range: 51-34°). Stretched penile length increased to 0.5-2.0 cm, and erect girth increased to 0.5-1.0 cm, with a correction of the hinge effect in four of four men. No adverse events such as skin changes, ulcerations, hypoesthesia, or diminished rigidity were reported.

***Vacuum devices***

When it comes to vacuum devices the same principles as traction devices are followed. Raheem *et al*[44], evaluated the efficacy of vacuum devices in an uncontrolled study assessing 31 patients. The vacuum device was applied over a 12-wk period (Osbon ErecAid, MediPlus, High Wycombe, UK) for 10 min twice daily. Penile pain was reduced significantly (*P* = 0.012). Stretched penile length also increased significantly (*P* = 0.029) with a mean of 0.5 cm. Reduction of the curvature was reported in 67% of patients. 10% had worsening curvature and 23% showed no change. Half of the patients were satisfied with the outcome while the remainder had their curvature corrected surgically. Vacuum therapy can improve or stabilize PD curvature, is safe to use in all stages of the disease, and could reduce the number of patients requiring surgery.

**COMBINATION THERAPIES**

In 1999, Mirone *et al*[45] prospectively examined patients treated with ESWT or ESWT and perilesional verapamil injections. A 52% improvement in plaque size by ultrasound was noted in the ESWT-only group compared 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[46]. A recent study by Palmieri *et al*[47] investigated the effects of extracorporeal shock wave therapy (ESWT) plus tadalafil 5 mg once daily in the management of patients with PD and erectile dysfunction who had not not previously been treated. One hundred patients were randomly allocated to receive either ESWT alone for 4 wk (*n* = 50) or ESWT plus tadalafil 5 mg once daily for 4 wk (*n* = 50). They concluded that ESWT and tadalafil 5 mg once daily may represent a valid strategy for the conservative management of selected PD patients complaining of ED as it significantly improves EF and QoL when compared to ESWT alone. However, ESWT plus tadalafil 5 mg once daily was not able to significantly improve plaque size and curvature degree in our subset of patients.

A placebo controlled study by Preito Castro *et al*[20] randomized 45 patients to receive vitamin E and colchicine or ibuprofen. Statistically significant improvements 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.

In 2002, Cavallini *et al*[22] randomized 60 men toreceive 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.

**CONCLUSION**

In our review we showed the “Status quo” on non-surgical treatment for PD (Table 1). Unfortunately no further substantial, quality evidence on the use of medical therapy currently exits. There is, however, an increasingly enhanced interest in this disorder and basic scientific and clinical research will eventually lead to a more effective methodology to study the disease. In the meantime, a consistent number of non-surgical treatment options that offer some benefit with respect to disease stabilization, alleviation, as well as reduction of deformity and improved sexual function are available. In conclusion the most beneficial treatment identified are: (1) oral treatment with potassium para-aminobenzoate (may result in a significant reduction in penile plaque size and penile pain as well as penile curvature stabilization); (2) Intralesional treatment with interferon (may improve penile curvature, plaque size and density, and pain); (3) iontophoresis with verapamil 5 mg and dexamethasone 8 mg ( may improve penile curvature and plaque size); and (4) Extracorporeal shock-wave treatment ( may be beneficial for penile pain and stabilization of plaque).

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**Table 1 Efficacy of non surgical treatments on Peyronie’s disease**

|  |  |
| --- | --- |
| **Therapy** | **Therapeutic Activity and Indication** |
| Oral treatment with potassium para-aminobenzoate. | Reduction in penile plaque size and penile pain as well as penile curvature stabilization |
| Oral treatment with vitamin E and tamoxifen | Not associated with significant reduction in penile curvature, plaque size or penile pain |
| Other oral treatments (acetyl esters of carnitine, pentoxifylline) | Not recommended |
| Intralesional treatment with verapamil | No statistically significant differences in plaque size, penile curvature, penile pain |
| Intralesional treatment with steroids | Not associated with significant reduction in penile curvature, plaque size or penile pain |
| Intralesional treatment with interferon | Improve Penile curvature, plaque size and density, and pain |
| Intralesional treatment with clostridial collagenase | Significant decreases in the deviation angle, plaque width and plaque length |
| Iontophoresis with verapamil 5 mg and dexamethasone 8 mg | Improve penile curvature and plaque size |
| Extracorporeal shock-wave treatment  | Beneficial for penile pain and stabilization of plaque |
| Topical verapamil gel 15%  | Improve penile curvature and plaque size |
| Penile traction devices and vacuum devices | Reduce penile deformity and increase penile length |
| Combination therapies | Preliminary evidences to be clarified |