Oral therapy for Peyronie's disease, does it work?

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Contributions: (I) Conception and design: All Authors; (II) Administrative support: R Wang; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All Authors; (V) Data analysis and interpretation: All Authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Peyronie's disease (PD) is a localized, wound-healing, connective tissue disorder of the penis characterized by scarring of the tunica albuginea. This fibrous inelastic scar leads to penile pain, penile deformity and erectile dysfunction (ED), and a difficulty performing coitus. Over the past several decades, a myriad of oral agents for the treatment of PD have been studied and suggested. While the gold standard of care remains surgical therapy, many physicians continue to prescribe oral and intralesional injections for treatment during the acute phase of the disease. This article seeks to summarize the different oral therapy agents for PD and the research associated with each medication. While the American Urological Association has not recommended most of the mentioned medications for the treatment of PD, two newer therapies have shown success and have the potential of becoming baseline treatments for the acute phase of PD.

Keywords: Peyronie's disease (PD); oral therapy; penile curvature

Introduction

Peyronie's disease (PD) is a localized, wound-healing, connective tissue disorder of the penis characterized by scarring of the tunica albuginea. This fibrous inelastic scar leads to penile pain, penile deformity and erectile dysfunction (ED) with difficulty in performing coitus. Francois de la Peyronie first described the condition in 1743 while he was the surgeon for Louis XIV of France. Although earlier studies reported an incidence of 0.3–0.7%, recent publications have shown an overall incidence of 3.2–8.9%, with more than 75% of cases occurring in men between 45 and 65 years of age (1,2). Of note, 10% of patients experience onset of symptoms before 40 years of age (2). Furthermore, the incidence of PD following radical prostatectomy is reported to be as high as 15.9%, and a recent study showed that penile curvature is a common finding (38.6%) at the time of inflatable penile prosthesis implantation surgery for ED after prostate cancer treatment (3,4).

The treatment for PD begins with a focused history and physical exam. A detailed history should assess information about the onset and duration of disease, associated traumatic etiology, degree of penile curvature, loss of length during erection, and subjective level of sexual function. With regards to subjective sexual evaluation, standardized questionnaires such as the International Index of Erectile Function (IIEF) allow for objective and subjective initial assessments and a tool for measuring efficacy during treatment. Physical examination of the genitourinary system should include penile length while stretched, plaque location, and size. The degree of curvature can be assessed by the patient taking photographs of the erect phallus or by vasoactive injections in combination with penile duplex Doppler ultrasound.

Understanding the natural history and pathogenesis of PD is important to selecting appropriate treatment regimens. While the pathophysiology is not completely understood, it is hypothesized that the inciting event is a subclinical traumatic tear to the tunica albuginea. The tear

Table 1 Oral agents for Peyronie's disease

Oral therapy	Mechanism of action	Notable side effects
POTABA	Decreases fibrosis and inhibits collagen formation by decreasing serotonin levels, increasing monoamine oxidase activity and inhibiting fibroblast glycosaminoglycan secretion	Acute hepatitis, hypoglycemia, GI distress, rash
Vitamin E	Inactivates free radicals, reduces oxidative stress	Cerebrovascular events, GI distress, headache, dizziness
Colchicine	Depolymerizes tubulin; inhibits cell mitosis, leukocyte adhesion and collagen transport	Nausea, diarrhea, abdominal pain, aplastic anemia
Tamoxifen	Modulates TGF-β release from fibroblast to diminish fibrogenesis	Hot flashes, ED, GI distress, alopecia, thromboembolism, pancytopenia
Carnitine	Inhibits acetyl coenzyme-A; increases mitochondrial respiration causing decrease in free radicals	GI distress, seizure, hypotension
Procarbazine	Alkylating chemotherapy agent	Cytotoxicity, myelosuppression, hepatotoxicity, fatigue, CNS disturbance, GI distress
Omega-3 fatty acids	Anti-inflammatory agent by limiting effects of eicosanoids	GI distress, fishy breath
PDE-5 inhibitors	Increases cGMP and nitric oxide causing fibroblast apoptosis and inhibition of collagen synthesis/deposition	Headaches, erections, dizziness, flushing, heart burn, blue vision, myalgia
Pentoxifylline	Phosphodiesterase inhibitor; prevents fibroblast proliferation and collagen/elastin deposition; increases fibrinolytic activity	Fatigue, GI distress, flushing, dizziness, headache

leads to a proliferative fibrotic reaction, resulting in an inelastic scar. The treatment for PD is separated into those within the acute phase and those in the chronic stabilization phase. The acute phase time is loosely defined as less than 12 months from the onset of symptoms. During this time, the patient's scar is continuing to modify and change. The chronic phase is determined once the patient's curvature has remained stable for at least 6 months. While surgical treatment remains the gold standard for PD, it is mostly offered to males in the chronic phase of the disease. For those patients in the acute phase, pharmacotherapy provides the potential to improve function, reduce deformity, and stabilize scar progression (5). Herein, we review the current available knowledge regarding oral treatment options for PD. It is important to note that while certain recommendations listed are based on evidence-based findings; others mirror expert opinion (*Table 1*).

Potassium para-aminobenxoate (POTABA)

POTABA is a compound known for its antifibrotic and anti-inflammatory properties that aid in treatment for fibrotic disorders such as dermatomyositis and scleroderma. Its efficacy is thought to be due to a reduction in collagen formation via decreasing serotonin levels, increasing monoamine oxidase activity, and inhibiting fibroblast glycosaminoglycan secretion (6). The first proposed use of POTABA to treat PD was in 1959 by Zarafonetis and Horrax (7). In 2005, Weidner *et al.* performed a multi center, randomized, double blind placebo-controlled trial of POTABA (51 patients) versus placebo (52 patients) in treatment naïve PD patients with non-calcified plaque. The trial arm received 3 g of POTABA orally, 4 times per day for 12 months. After 12 months, patients on POTABA had significant improvement in penile plaque size compared to those on placebo. In addition, patients receiving placebo were noted to have worsening of their curvature. The authors concluded that POTABA may aid in the stabilization of scar tissue, which would prevent progression of curvature (6). There have been no further randomized control trials to evaluate the efficacy of POTABA. This is perhaps due to its side-effect profile, which includes gastrointestinal distress, diarrhea, acute hepatitis, and hypoglycemia (8).

Vitamin E

Vitamin E, a fat-soluble antioxidant, inactivates free radicals that saturate nitric oxide (NO), thereby keeping active NO levels elevated to allow proper wound healing. By limiting oxidative stress, it potentially also offers an anti-inflammatory effect. It was first described for the treatment of PD in 1948 (9) and, due to its low cost and availability, remains the most frequently prescribed oral agent for PD (10). Despite its use over the past seven decades, multiple placebo-controlled designs have shown no significant improvement in pain, degree of curvature, plaque size, or ability to have intercourse. In 1983, Pryor and Farrell completed a double-blind, placebo-controlled trial of vitamin E in 40 PD patients, and found no significant improvement in plaque size or penile curvature (11). Furthermore, a more recent study in 2007 by Safarinejad *et al.* provided the largest trial to date evaluating vitamin E for PD. The authors compared vitamin E alone and in combination with L-carnitine to placebo in 236 men with early chronic PD; classified as patient with pain during erections, penile curvature not interfering with vaginal penetration, non-painful palpable scar, hyperechoic lesion on penile ultrasound, absence of calcification, and total plaque area <2 cm^2. Group 1 (58 men) received vitamin E 300 mg orally twice a day. Group 2 (59 men) received propionyl-L-carnitine, 1 g orally twice a day. Group 3 (60 men) received vitamin E 300 mg orally twice a day as well as propionyl-L-carnitine 1 g orally twice daily. Lastly group 4 received a similar regimen of placebo during the 6-month trial period. After therapy, there was no significant change in reduction of penile curvature between the four groups (P=0.9), nor any decrease in plaque size (P=0.1) (12).

Despite lack of evidence proving vitamin E efficacy, it is still frequently prescribed and oftentimes given concurrently with other treatment modalities with hopes of a synergistic role. Common adverse effects from vitamin E use include nausea, vomiting, diarrhea, and increased risk for prostate cancer and cerebrovascular events (13).

Colchicine

Although colchicine is mostly known for its treatment of gout, it also exhibits properties that aid in the treatment of PD. Colchicine depolymerizes tubulin, thereby inhibiting cell mitosis, leukocyte adhesion, and collagen transport. Applying this property, colchicine should theoretically diminish wound contraction by inhibiting collagen deposition (14). Most studies evaluating colchicine have described some improvement in curvature, but these studies were not randomized, nor did they provide objective measurement for definition of improvement. Safarinejad *et al.* proved to be one of the few trials that evaluated the therapeutic effects of colchicine by completing a single center, randomized, double-blind, placebo-controlled trial of 84 PD patients without calcified plaques (15). Patients in the colchicine arm were treated with 0.5–2.5 mg colchicine daily for 4 months. At the end of the trial, the colchicine group did not demonstrate objective improvement in penile curvature or plaque size. Other studies have evaluated the synergistic effects of colchicine with vitamin E. Prieto Castro *et al.* reported significant improvement in plaque size and penile curvature in patients using daily vitamin E and colchicine compared to ibuprofen alone (16). Of note, there were only 45 patients in this trial and there was no placebo arm. However, a subsequent retrospective study of 100 men exposed no statistically significant differences in efficacy for pain relief, penile curvature, or plaque size between colchicine and colchicine combined with vitamin E (17).

Tamoxifen

Tamoxifen is a non-steroidal estrogen receptor antagonist. In the treatment of PD, it has been shown to diminish fibrogenesis in the tunica albuginea via modulating the release of TGF-β released from fibroblast (18). Ralph *et al.* first proposed its treatment in 1992 as a result of an uncontrolled study that demonstrated improvement in penile deformity for 11 out of 31 men. However, these finding were not reproducible when tamoxifen was evaluated in a prospective, placebo-controlled trial in 25 patients with PD without calcified plaques. Despite the use of 20 mg tamoxifen twice daily, there was no significant improvement in pain, curvature, or plaque size when compared to placebo (19).

Carnitine

Carnitine is an inhibitor of acetyl coenzyme-A that allows for the decrease of free radical formation during times of cell stress. In 2001, Biagiotti *et al.* performed a randomized trial of 96 PD patients to L-carnitine versus tamoxifen. Results showed significant penile curvature improvement in the L carnitine group (20). As aforementioned, the Safarinejad 2007 4-arm trial (vitamin E, carnitine, vitamin E and carnitine, and placebo) proved no significant improvement in penile curvature, plaque size, or pain (12).

Omega 3 fatty acid

Similar to other oral agents, omega-3 fatty acids have been evaluated in the treatment of PD due to its known anti-inflammatory properties. In 2009, Safarinejad *et al.* published their results on a prospective, randomized double-blind omega-3 fatty acids versus placebo trial. A total of 224 patients with early chronic stage PD were randomized to 1.84 g of daily omega-3 supplementation versus placebo for 6 months. Patients were assessed with IIEF-5 and PDDU before and after the 6 months of medication. Unfortunately, there was no significant improvement with regard to plaque volume, penile curvature, pain during erection, and erectile function (21). Currently, there is a lack of data to support a beneficial effect of omega-3 supplementation in early-chronic stage of PD.

Procarbazine

Procarbazine is an alkylating chemotherapy drug often used to treat CNS lymphoma, Hodgkin's lymphoma, and high-grade gliomas. In 1968, Aron *et al.* noted a regression of Dupuytren's disease in patients undergoing treatment of Hodgkin's disease with procarbazine, thereby suggesting its use in a disease with proliferation of connective tissue (22). With this premise, in the 1970s, Byström proposed procarbazine for the treatment of PD, but subsequent studies did not reveal any objective benefit. In addition, studies unveiled significant side effects of the cytotoxic medication, and it was recommended to not be used in the benign disease of PD. Side effects include myelosuppression, hepatotoxicity, fatigue, GI distress, and CNS disturbance (23,24).

Phosphodiesterase type 5 inhibitors (PDE-5 inhibitors)

Although PDE-5 inhibitors are commonly thought as a treatment for ED, recent studies have shown its potential use in the treatment of PD in patients with or without ED. PDE-5 inhibitors increase cyclic guanosine monophosphate (cGMP) by inhibiting the degradation of cGMP to GMP. With the increase of cGMP and NO, collagen synthesis and deposition are inhibited and apoptosis of fibroblast and myofibroblast occurs (25). Due to this property, PDE-5 inhibitors may prove to be advantageous for scar remodeling. In a rat model of PD, sildenafil was shown to cause significant reduction in the collagen-to-fibroblast ratio

in the tunica albuginea as well as plaque size (25). Chung and colleagues study the use of tadalafil for treatment of PD in human subjects. They reported that 2.5 mg tadalafil daily for 6 months resulted in resolution of septal scar in 69% (24/35) of patients without palpable penile plaque. Only 10% of the non-treatment arm noted resolution of scar. It is important to mention that the septal scar was not clinically palpable and most patients in this study did not have curvature (26). More recently, a 2014 study reported treatment outcomes of patients with PD using 50 mg sildenafil daily or 400 IU vitamin E for 3 months. After 12 weeks, both groups showed similar reduction in plaque volume and penile curvature that was statistically significant. The differences between the two groups, however, were not statistically significant. The sildenafil cohort did show statistically significant improvement in IIEF scores and pain reduction compared to vitamin E alone (27). A large-scale double blind placebo trial would need to be done and validate the clinical benefit of PDE-5 inhibitor, but current research is promising (*Table 2*).

L-arginine

L-arginine is a NO precursor that stimulates NO synthase. This causes an increase in NO, as well as a reduction in fibroblast due to apoptosis. These two properties are thought to be the mechanisms behind L-arginine as an antifibrotic agent (25). As aforementioned, Valente *et al.* evaluated penile plaques in rat models treated with PDE-5 inhibitors, but also with l-arginine. Similarly to PDE-5 inhibitors, L-arginine exhibited significant reduction in plaque size as well as collagen to fibroblast ratio (25). A later study by Medeiros *et al.* demonstrated that arginine also has a protective effect against scar tissue formation when submitting the penis of rats to pelvic radiation (28). In 2012, Abern *et al.* noted a trend toward curvature improvement in PD patients treated with penile traction therapy in conjunction with intralesional verapamil, oral L-arginine and oral pentoxifylline (PTX) (29). While this study has numerous variables that could contribute to curvature improvement, it proves to be one of the few human trials in which L-arginine was used to treat PD. Given these findings, L-arginine may prove to be a valuable treatment options for PD, but further human trials are needed.

Pentoxifylline (PTX)

Although most of the oral medications investigated for

Table 2 Studies of PDE-5 inhibitor treatment for Peyronie's disease

Study	Design	N	Therapy	Duration	Outcome	Level of evidence
Chung *et al.*, 2011	Retrospective review of prospective database	65	2.5 mg tadalafil or placebo	6 months	Tadalafil showed statistically significant improvement in IIEF score. Sixty nine percent of tadalafil patients showed resolution of septal scar on PDDU (most patients in this study did not have penile curvature)	IV
Ozturk *et al.*, 2014	RCT-unblinded, not placebo controlled	39	50 mg sildenafil daily or 400 IU vitamin E daily	3 months	Significant improvement in plaque volume and curvature in both groups (assessed by PDDU); differences between both groups were not statistically significant; sildenafil showed statistically significant improvement in IIEF scores and pain reduction compared to vitamin E alone	II

N, number of participants in study; RCT, randomized control trial; PDDU, penile duplex Doppler ultrasound.

the treatment of PD have shown poor or indeterminate outcomes in controlled studies, PTX has fared much better. PTX is a xanthine derivative that functions as a nonspecific phosphodiesterase inhibitor with known anti-inflammatory and anti-fibrogenic properties (30). It has been proposed for treatment of PD due to an *in vitro* study showing it prevents tunica albuginea fibroblast proliferation, attenuates TGF-B mediated deposition of collagen, reduces deposition of elastin, and increases fibrinolytic activity (31-33). Given these properties, a 2010 double blind, placebo-controlled study sought to determine the effect of PTX in patients with early chronic PD (30). Two hundred twenty-eight patients were randomized to receive 400 mg of PTX sustained release versus placebo for 6 months. Most participants had failed at least one previous PD treatment. The placebo group was 4 times more likely (42%) to have disease progression compared to the treatment arm (11%). Furthermore, the PTX group showed significant improvement in both objective and subjective measures; (I) improvement in penile curvature as measured by duplex ultrasound before and after corporal injection with prostaglandin E1; (II) plaque volume and (III) IIEF scores (30). More recent studies have evaluated oral PTX in conjunction with oral antioxidants, intralesional PTX and intralesional verapamil with varying results (34,35). While PTX remains a strong competitor for PD treatment, further large multi-center trials will need to be concluded to ensure

results are reproducible (*Table 3*).

Conclusions

Despite decades of PD research, the definitive etiology and pathophysiology have not been completely elucidated. While surgical therapy remains the gold standard for chronic severe PD, there is a myriad of other less invasive treatment options, namely oral and intralesional medications. Herein, we have reviewed the mostly commonly prescribed or discussed oral agents for treatment of PD. Although a number of well-designed studies have discovered positive responses with oral medication, their small sample size limits the power and reproducibility of the study. Currently, the American Urological Association guidelines state clinicians should not offer oral therapy with vitamin E, tamoxifen, omega-3 fatty acid or combination of vitamin E with L-carnitine. Similarly, the 2010 International Consultation on Sexual Medicine did not support the routine clinical use of oral agents for PD (5). Two oral medications not restricted by the guidelines are PDE-5 inhibitors and PTX. Further research on PDE-5 and PTX, to include large multi center double blind, randomized-control trials, are needed to determine their efficacy. Both medication classes give hope to the absence of allowed oral medications for the treatment of PD.

Table 3 Studies of pentoxifylline treatment for Peyronie's disease

Study	Design	N	Therapy	Duration	Outcome	Level of evidence
Safarinejad *et al.*, 2010	RCT—double blind, placebo controlled	228	400 mg pentoxifylline twice daily compared to placebo	6 months	Significant improvement in penile curvature and plaque volume as assessed by PDDU; improvement in IIEF scores and significantly less progression of disease compared to placebo	II
Smith *et al.*, 2011 (36)	Retrospective cohort study	71	62 patients received 400 or 800 mg of pentoxifylline 3 times daily; nine patients received vitamin E or no treatment	1 year	Statistically significant stabilization or improvement in calcium burden within plaque, as assessed by ultrasound, in pentoxifylline arm	IV
Alizadeh *et al.*, 2014	Quasi experimental	90	30 patients received pentoxifylline 400 mg 3 times daily; the remaining patients were subjected to intralesional injections or a combination of treatments	6 months	26.7% curvature reduction, 30% plaque size reduction, 73% pain reduction. No clear definition on how outcomes were objectively measured	IV

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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