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Oral therapy for Peyronie's disease

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Peyronie's disease (PD) remains a therapeutic dilemma for the urologist. Despite a myriad of medical therapies proposed for PD there have been limited advances in oral medical treatment. Several new approaches are presented which hold promise of success, although a definitive medical therapy for PD has yet to be established. Since early stage disease is reputed to respond better than well-established plaques, an early trial of inexpensive, safe and well-tolerated oral therapy is often initially recommended. This review discusses the historical aspects as well as contemporary oral medical therapy for PD. With advances in the molecular biology of inflammation and wound healing, the management and understanding of this frustrating disease will no doubt improve.
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Introduction

Peyronie's disease (PD) affects 1–3% of the male population.[1,2] PD is a benign condition of the penis with a pathogenesis based on trauma induced disruption of tunica albuginea fibers of the corpora cavernosa. Greater than 75% of patients with PD are between 45 and 65 y of age. In this aging population the modulus of elasticity of tunical and septal tissues is diminished.[3] The rationale for oral systemic therapy for localized disease is based on the linkage with other conditions associated with loss of elasticity.

Peyronie's disease has been linked to systemic conditions such as hypertension and diabetes.[2] PD is associated with Dupuytren's disease (palmar aponeurosis), Ledderhose's disease (plantar aponeurosis), Paget's disease and knuckle pads.[4,5] An immunologic component to Peyronie's disease has been proposed.[6] These associations lend credence to using systemic oral therapy for this disease.

Historical perspective

A multitude of oral treatments for Peyronie's disease have evolved in a fairly random fashion following the prevailing medical therapy for other diseases. Historically, substances such as mercury and mineral water, potassium iodide, bromides and hyperthermia, sulphur, copper sulphate, salicylates, estrogens, thiosinamin, acidification with disodium phosphate, arsenic, fibrinolysin and milk have been suggested as oral or topical agents for Peyronie's disease.[7,8] Of particular historical note is the early success of procarbazine (Natulan), a cytotoxic alkylating agent used for the treatment of Hodgkin's disease. Encouraged by success in the treatment of Dupuytren's contractures, a series of studies were conducted which led to the report of complete remission in over half the patients given the drug for established plaques.[9] These promising results were later countered by reports of toxicity to the testicular germinal epithelium with resultant azospermia.[10]

Modern oral therapy approaches to Peyronie's disease have their foundation in early work, which examined the ability to pharmacologically manipulate wound healing. Several studies evaluated the ability of vitamin E and colchicine to alter collagen content in scar tissue of animal models as well as patients with scleroderma, flexor tendon adhesions and urethral stricture disease.[11] The hypothesis proposed suggested these conditions were associated with poorly-crosslinked collagen that was susceptible to degradation by collagenase, and that colchicine stimulated collagenase activity. Perioperative colchicine was demonstrated to decrease keloid re-formation after excision of the keloid scar.[12]

Immunomodulating agents such as Potaba have been utilized in Peyronie's disease to combat the

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inflammatory reaction in the areolar tissue found between the tunica albuginea and the corpus cavernosum. This reaction matures into fibrotic tissue rich in hyaluronic acid and abnormal elastic fibers.[13]

The extensive variety of treatment regimens employed over the years bears proof to the difficulty physicians have faced in treating a disease where the cause is unknown. Additionally, while PD is a useful term for acquired penile pain and/or deformity, it is not clear that the spectrum of disorders develop by the same mechanism. In order to adequately assess any therapy option (including oral therapies) a common endpoint or set of criteria should be employed. A review of the literature reveals a lack of reproducible, objective documentation of the parameters of disease severity before and after therapy. Finally, the issue of spontaneous resolution and tendency for improvement has been commonly cited.[14–17] An appropriate oral therapy should be evaluated for success in treating inflammatory changes (ie pain, tenderness) as well as fibrotic deformities (ie palpable plaques, curvature). In our search of the literature this distinction was infrequently seen.

This article will review the evolution of contemporary oral therapies including vitamin E, potaba, colchicine and tamoxifen (Table 1). Unfortunately, most of these studies are non-randomized and uncontrolled by design. The few reported placebo arms demonstrate significant improvement in pain (75%), penile curvature (42%) and plaque size (25%), suggesting the need for caution in interpreting uncontrolled studies.[18]

Vitamin E

Antioxidants such as vitamin E prevent fibrosis. Early studies on the use of vitamin E in Peyronie's disease reported a decrease in penile curvature in 78% of patients and a decrease in plaque size in 91%.[10,19,20] A survey of results reported in the literature between 1952 and 1982 suggested response rates between 0 and 70%.[21] Devine *et al* reported resolution of plaques (20%) and penile curvature (33%) with vitamin E therapy.[22] However, with additional follow-up of a larger cohort, they subsequently reported that while 99% of patients experienced a decrease in pain, 70% noted no objective improvement (Table 2).[23]

Pryor and Farrell reported that 35% of patients taking vitamin E noted an improvement in penile pain, however minimal effects on plaque size or penile curvature could be expected.[24] Gelbard *et al* evaluated patient's perception of their disease in a questionnaire survey.[1] They detected no difference between those patients treated with vitamin E and those untreated with respect to overall improvement (22% *vs* 19%), improvement in curvature (11% *vs* 11%) or improvement in pain (53% *vs* 44%). More untreated patients characterized their disease as one of gradual resolution (14%) than those treated with vitamin E (9%).

Though the body of evidence does not support a strong efficacy for vitamin E, the low toxicity and expense of the supplement encourages its use either alone or in combination with other oral, intralesional or surgical modalities.[8]

Potaba (potassium para-aminobenzoate)

Potaba has been utilized in a variety of conditions characterized by chronic inflammation and fibrosis, including scleroderma, dermatomyositis, morphea, pulmonary fibrosis and Peyronie's disease.[25] Potaba inhibits abnormal fibroblast proliferation, acid mucopolysaccharide and glycosaminoglycan secretion.[26,27] The anti-inflammatory activities of Potaba may depend on initial biotransformation by activated granulocytes through the myeloperoxidase pathway.[28]

The results of Potaba therapy for Peyronie's disease are summarized in Table 3. In a questionnaire survey of 1854 men treated for at least 3 months with Potaba (12 g), Hasche-Klunder reported

Table 2 Results with vitamin E therapy for Peyronie's disease

Study	*Patients*	*Improvement in pain*	*Improved plaque size*	*Improved angulation*
Scardino[20]	23	100%	91%	78%
Chesney[10]	58	82%	82%	Not reported
Pryor[24]	40	35%	Minimal	10%
Devine[22]	107	99%	20%	33%

Table 1 Oral therapies for Peyronie's disease

	Brand name	*Dosage*	*Side-effects*
Vitamin E	Not applicable	200 i.u. b.i.d.	None reported
Potassium para-aminobenzoate	Potaba	12 g	GI
Colchicine	Colbenemid	0.6 mg t.i.d. 1.2 mg b.i.d.	GI (33%), fever, rash, agranulocytosis, aplastic anemia, myopathy, angioneurotic edema
Tamoxifen	Nolvadex	20 mg b.i.d.	Hot flushes, decreased libido, decreased ejaculatory volume

Table 3 Results with Potaba therapy for Peyronie's disease

Study	Patients	Improvement in pain	Improved plaque size	Improved angulation
Zarafonetis[41]	21	100%	76%	82%
Hasche-Klunder[29]	25	100%	100%	71%
Riley[42]	18	100%	11%	75%
Carson[43]	32	44%	56%	58%

69% of men improved and 13% of men were 'cured'.[29] Unfortunately none of these studies were placebo controlled and none included baseline or post-therapy objective measurements of angulation or plaque size.

Carson retrospectively reviewed 32 patients who were treated with Potaba (4 g t.i.d.) for a minimum of 3 months and were followed for a mean of 14.4 months.[30] He reported improvement in penile discomfort (44%), plaque size (56%) and penile angulation (58%). Complete resolution of penile angulation was observed in 26% of patients. The average interval to improvement was 4.2 months, and younger patients with a shorter duration of disease were more likely to respond to therapy. While this study was retrospective and uncontrolled, it does suggest a potential role for Potaba in the medical therapy of Peyronie's disease. Unfortunately, the results were not reported as an intent-to-treat study and the number of patients who started therapy but discontinued prior to 3 months was not provided. The high cost of Potaba, frequent dosing requirement and potential for severe gastrointestinal side-effects limit its use.[30]

Colchicine

Colchicine is an alkaloid derived from the autumn crocus, *Colchicum autumnale*. The primary action of colchicine is to bind tubulin, which inhibits the formation and function of the mitotic spindle during mitosis. However, colchicine's effect on microtubules has an impact on many other cell functions.

Procollagen is synthesized in the rough endoplasmic reticulum (RER) of fibroblasts, it is then transported to the golgi apparatus before vesicular transport to the cell surface where it is converted to collagen by procollagen peptidase.[31] Microtubules provide the infrastructure for this transcellular vesicle transport, and colchicine interferes with microtubular structure and function.[32] Microtubular function is also important for phagocytic activity in the inflammatory response, possibly explaining colchicine's anti-inflammatory activity.[33] Colchicine may also inhibit the secretion of inflammatory cytokines and block the formation of eicosanoids by inhibiting phospholipase A2 in monocytes and neutrophils.[34,35]

Table 4 Results with colchicine therapy for Peyronie's disease

Study	Patients	Improvement in pain	Improved plaque size	Improved angulation
Akkus[38]	24	78%	50%	37%
Kadioglu[34]	60	95%	NR	30%
Flores[35]	59	71%	47%	55%

Intracellular collagen exists as fibrous-long spacing collagen (FLS) within the RER in fibromatoses including Peyronie's disease, Dupuytren's contracture and musculoaponeurotic desmoid fibromatosis.[31] Colchicine has been shown to cause collapse of the RER, decrease in myofibrils and decrease in intracellular FLS collagen in fibromatoses disease states.[31] Colchicine stimulates collagenase production and activity and decreases collagen synthesis.[2,11]

Colchicine has been demonstrated to inhibit *in vitro* proliferation of fibroblasts cultured from Peyronie's plaques as well as normal adjacent tunica albuginea from the same patients.[36] El-Sakka *et al* evaluated the effects of colchicine in an animal model of Peyronie's disease.[37] They demonstrated that colchicine-treated animals exhibited less collagen deposition in the tunica albuginea. Decreased elastic fiber fragmentation and down-regulation of TGF-β1 protein expression was also noted with colchicine, but only with early initiation of therapy. They hypothesized that poor tissue levels may be obtained with delayed therapy, due to dense extracellular collagen deposition preventing perfusion to the diseased area. In summary, colchicine acts in both inflammatory and collagen production (fibrotic) phases of Peyronie's disease.

Results from clinical trials with oral colchicine are summarized in Table 4. Akkus *et al* reported that 78% of patients experienced a reduction in pain, 26% noted a marked decrease in penile curvature and an additional 11% noted a slight decrease in penile curvature with a mean of 9-months of oral colchicine therapy.[38] This study was one of the first to use ultrasonographic measurement of plaque size and penile angulation after intracavernous injection as objective measures of response. While 33% of patients experienced gastrointestinal side effects (diarrhea, nausea), only 17% discontinued therapy.

Kadioglu *et al* evaluated the efficacy of oral colchicine in men during the acute phase of disease (mean 5.7 months duration).[34] They noted a 95% resolution of pain, however objective measures of penile curvature with intracavernosal injection improved in only 30% of men, while deteriorating further in 22% of men. A gradual dose escalation protocol, starting with 0.5 mg daily and increasing to 1.0 mg twice daily, may have improved gastrointestinal tolerance as only 2% of patients discontinued therapy due to side-effects. Treatment duration was 3–6 months. Patients with short duration disease,

no erectile dysfunction and curvature $< 30^{\circ}$ were more likely to respond to therapy.

Tamoxifen

Tamoxifen is a non-steroidal antiestrogen that has been proven effective in the treatment of desmoid tumors. Tamoxifen is believed to impact the inflammatory response through modulation of TGF-β1 secretion from fibroblasts.[39] TGF-β has been shown to be involved in a complex sequence of monocyte actions including, chemo-attraction, controlling the production of cytokines and induction of angiogenesis. Additionally, TGF-β stimulates the synthesis of connective tissue matrix while simultaneously inhibiting the synthesis of matrix degrading proteases.[18]

An early study treated men for 3 months with 20 mg of tamoxifen twice daily.[39] They reported improvements in pain (80%), plaque size (34%) and penile curvature (35%). Patients with short duration disease (< 4 months) were more likely to note improvement in plaque size. Maximum response was noted at 6 weeks of therapy. The degree of cellular inflammation was determined by plaque biopsies prior to therapy in 12 patients. Patients with evidence of inflammatory infiltrate were more likely to respond to tamoxifen therapy (75%) than those with no evidence of inflammation (0%).

In one of the few randomized, placebo-controlled studies of oral therapy for Peyronie's disease, Teloken *et al* reported no significant differences between tamoxifen and placebo with regards to improvement in pain (67 *vs* 75%), plaque size (31% *vs* 25%) or penile curvature (46% *vs* 42%).[18] No difference in objective measures of ultrasonographic plaque size or penile curvature following intracavernosal injection was detected. Results are summarized in Table 5.

Other anti-inflammatory therapies

Non-steroidal anti-inflammatory agents might impact the inflammatory phase of Peyronie's disease. El-Sakka *et al* evaluated the impact of ibuprofen on an animal model of Peyronie's disease. They could not demonstrate any inhibitory effect on TGF-β1 expression, elastic fiber fragmentation or collagen deposition.[37] Histologic evaluation of the tunica albuginea and areolar tissue between the tunica and corpora cavernosa have demonstrated an increase in mast cell concentration, specifically around the fibrous plaques and areas of granulation.[40] This suggests that medical therapy during the early phase of PD aimed at suppressing mast cell activation and proliferation may be of benefit.

Table 5 Results with tamoxifen therapy for Peyronie's disease

Study	*Patients*	*Improvement in pain*	*Improved plaque size*	*Improved angulation*
Ralph[39]	36	80%	34%	35%
Teloken[18]	25	67%[a]	31%[a]	46%[a]

[a]Non-significant versus placebo-controlled patients.

Conclusion

The basis for oral therapy in Peyronie's disease has been founded in anecdotal, poorly designed retrospective studies. Rigorous long-term evaluations using randomized, double-blinded, placebo-controlled design, and pre/post-therapy visual analog pain scales, standardized sexual questionnaires, and objective measurement of plaque size with degree of angulation are needed. The impact of precise study design on interpretation of results can be appreciated in recent studies of PD.[18]

The role of oral medication to alter the course of Peyronie's disease may be limited to the 12–18 months of plaque maturation during which time penile pain and induration (ie inflammatory phase) is gradually resolving. Once stable non-painful penile curvature has been established, the likelihood of measurable success with oral therapy appears limited. As the molecular biology of inflammation and wound healing is elucidated, new approaches for medical intervention will no doubt be available for therapy of PD. Promising areas for investigation include: modification of fibroblast function, growth factor activity, extra cellular matrix deposition and cytokine modulation. Whether these molecular advances can be tailored into oral therapy remains to be seen.

Since the rate of spontaneous resolution appears variable at best, the results of oral therapy should be carefully compared in placebo-controlled studies over the duration of currently held disease natural history timelines. However, faced with the alternatives of intralesional therapy or surgical intervention, many men will chose an initial trial of oral therapy.

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