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Contemporary Review of Treatment Options for Peyronie's Disease

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Abstract:

Peyronie's disease (PD) is a penile wound-healing disorder resulting in fibrotic plaque in the tunica albuginea, likely resulting from micro trauma. Due to variable disease presentations, a myriad of proposed treatment options, physician misconceptions about the disorder, and severe psychological distress in afflicted patients; PD can be a difficult to manage entity. This review seeks to provide a current and comprehensive overview of oral, topical, intralesional, mechanical, and surgical therapies for PD.

Keywords: Peyronie's Disease, Penile curvature, Penile plaque, Intralesional injection, Penile straightening, Penile prosthesis.

Abbreviations:

PD: Peyronie's disease

TGF: Transcripton Growth Factor

TIMPs: Tissue Inhibitors of Metalloproteinases

PDE5-i: Phosphodiesterase Type 5 Inhibitor

ILI: Intralesional Injection

CCH: Collagenase Clostridium Histolyticum

ADSC: Adipose Derived Stem Cells

ESWT: Extracorporal Shock Wave Therapy

ED: Erectile Dysfunction

PTT: Penile Traction Therapy

TAP: Tunica Albuginea Plication

PIG: Plaque Incision and Grafting

PEG: Plaque Excision and Grafting

SIS: Small Intestinal Submucosa

IPP: Inflatable Penile Prosthesis

Introduction:

Peyronie's disease (PD) is a penile wound-healing disorder of the tunica albuginea resulting in fibrosis that can cause penile curvature, narrowing, shortening, hinging, pain, and inability to participate in penetrative sex. The reported incidence of PD is 3-10%[1,2]. The prevalence may actually be higher as men are often reluctant to seek treatment due to embarrassment. Some men are not significantly bothered by their

deformity and others lack knowledge of the condition and available treatment options. Urologists may continue to see more men presenting with PD as awareness of the disease and marketing for injectable agents continues to increase.

PD is often associated with significant psychosocial distress. It can be a difficult to manage entity with a confusing array of potential treatment options, many of which lack data in support of meaningful benefit. Primary care physicians and urologists have demonstrated incorrect assumptions about the prevalence and natural history of PD which can negatively affect diagnosis and treatment[3]. In this review, the authors seek to provide a comprehensive overview of the available medical and surgical treatment options for PD, focusing on the most effective treatment modalities and recent treatment advances.

A. Natural History and Etiology:

PD develops when fibrotic scar (Peyronie's plaque) develops in the tunica albuginia of the penis. The tunica albuginea is composed of an inner circular layer and outer longitudinal layer, both of which rely on a strong network of type 1 collagen and elastin[4]. Anchor sites of the tunica albuginea, especially along the dorsal septum, are susceptible to traumatic insults and vascular injury. Interestingly, the majority of men seeking treatment for PD do not recall a specific traumatic event. Instead, it is theorized that high intracavernosal pressures during sex may result in a sudden stretch on the tunica albuginia which exceeds its elastic capacity resulting in a microfracture. In response to such trauma, inflammatory cells (macrophages, neutrophils, mast cells) release inflammatory mediators, including cytokines, transcription growth factor (TGF)-

β, TGF-α, heparin binding epidermal growth factor, fibroblast growth factor, and collagenases. In patients with normal wound healing, fibroblast migration and deposition of type I and type III collagen occurs within days and, within weeks, a remodeling phase of collagen synthesis and degradation occurs. An appropriate balance of degradation by matrix metalloproteinases (collagenases) and inhibition of degradation by tissue inhibitors of metalloproteinases (TIMPs) is essential to prevent longstanding fibrosis. One of the important characteristics of PD is an imbalance in this wound healing process; Peyronie's plaques are highly enriched with TIMPs. This imbalance may occur in response to oxidative stress and overexpression of TGF-β, platelet derived growth factor, and/or fibroblast growth factor[5-10].

The acute phase of PD is often associated with painful erections and changing deformity/curvature of the penis during the erect state. This phase can last from 6-18 months. Spontaneous regression is rare. The goal of treatment during the acute phase is to relieve symptoms of pain, mitigate scar formation, and prevent worsening penile curvature/deformity. The subsequent chronic phase of PD is typically more quiescent with resolution of pain and stabilization of the plaque and deformity. The goal of treatment in the chronic phase is to correct deformity and induce straightening to allow for penetrative sexual intercourse while also maintaining as much penile length as possible[11,12].

B. Medical Therapies:

Non-surgical therapies for PD may be appropriate as first line options for symptomatic men in the acute phase of PD with unstable deformity and/or pain or in men with chronic

phase PD who are poor surgical candidates or are not ready to consider surgical correction. A myriad of nonsurgical therapies have been proposed for use in PD. Unfortunately, medical therapies are backed by limited evidence of benefit.

1. **Oral Medications:**

Given the inherent ease of administration and theoretic ability to provide balanced tissue penetration in the tunica albuginea, numerous oral agents have long been studied in patients with PD. Potoba, Vitamin E , procarbaizine, colchicine , L-carnitine , pentoxifylline, tamoxifen, omega-3 fatty acids , coenzyme Q10, and phosphodiesterase type 5 inhibitors (PDE5-i's) have all been trialed in PD patients[13]. Some experts recommend the use of pentoxifylline, L-arginine, and/or PDE5-i's as oral therapy for PD based on elegant animal model studies showing anti-fibrotic qualities associated with enhanced local nitric oxide levels[14]. Unfortunately, human trials of oral agents are uniformly limited by small sample size and, to date, no single oral agent has shown a clinically meaningful or lasting benefit in a large randomized controlled trial. Furthermore, many of these agents have significant side effect profiles. A summary of mechanisms, available evidence, and side effects of oral agents trialed in PD patients is available in Table 1. Currently, in agreement with the most recent recommendations by the International Consultation on Sexual Medicine, the authors do not routinely recommend oral agents as monotherapy in the treatment of PD[11].

2. Topical and Injection Therapies:

Numerous topical agents have been trialed for use in PD, including Beta-aminopropionitrile, liposomal recombinant human superoxide dismutase, and topical

verapamil[32-34]. Similar to oral therapy studies, these trials have been limited by sample size and lack of appropriate objective measures. Although early studies of verapamil showed promising results, subsequent analysis of tunical biopsies after topical verapamil therapy revealed that the drug is unable to penetrate the tunica albuginea at a detectable level[35]. Topical compound therapies utilizing pharmacologic tissue penetration enhancers represent an intriguing area of ongoing research. Recently, a small placebo controlled trial of topical nicardipine and superoxide dismutase compounded with emu oil in 22 men with untreated acute phase PD demonstrated significant improvement in multiple PD parameters (length gain, curvature reduction, pain scores) compared to placebo [(36)]. Larger controlled trials are needed to validate these findings.

To date, pharmacologic agents have been most effective when adequate concentrations are able to penetrate the tunica albuginea with electromotive assistance via iontophoresis or via intralesional injection (ILI). Iontophoresis utilizes application of an electrical field to facilitate penetration of a topical drug into the tunica albuginea. Detectable drug levels in the tunica albuginea after iontophoresis have been confirmed by biopsy[37]. In an unblinded study of 96 PD patients randomized to iontophoresis with verapamil (5mg) + dexamethasone vs placebo (lidocaine), the verapamil group had improved curvature from 43^0 to 21^0[38]. More recently, a double-blind placebo controlled trial of verapamil (10mg) iontophoresis vs placebo (saline) showed reduced curvature in both groups[39]. Future analysis will be required to determine if electrical current alone can induce plaque remodeling. Although some evidence for benefit exists, transdermal iontophoresis for the treatment of PD is not utilized widely.

ILI therapies have become the most promising non-surgical treatment option for durable improvement in PD symptoms and curvature. Corticosteroids were the first ILI therapy used for PD but had unfavorable side effects and did not result in any significant measured improvement in curvature, plaque size, or sexual function[40]. More recently, in multiple small trials, ILI verapamil has resulted in decreased curvature, resolution of narrowing deformity, reduction of plaque volume, and improvement in sexual function. Most notably, over 90% of patients experience resolution of pain[41,42]. In the largest ILI verapamil trial (156 PD patients) to date, ILI verapamil resulted in decreased curvature (mean reduction 30^0, range 5^0- 90^0) in 60% of patients and improved sexual function in 71% of patients at mean follow up of 30.4 months[43]. In contrast, a separate randomized trial of 80 PD patients treated with ILI verapamil vs saline found no significant difference in curvature, plaque size, or sexual function[44]. Variable results in these trials may be due to injection technique, patient selection (plaque size, plaque calcification, degree of curvature), or drug concentration. A randomized trial of 77 PD patients evaluating three different verapamil concentrations found the greatest improvements in plaque size, penile curvature, sexual function, and pain reduction in patients receiving 10mg/20ml ILI therapy[45]. Nicardipine, a dihydropyridine type calcium channel blocker, has also been used as an ILI agent for PD. Although not as thoroughly investigated as verapamil, a trial of 74 PD patients randomized to nicardipine (10mg/10ml) vs placebo showed improved sexual function and significant reductions in curvature, pain, and plaque size[46].

Interferon α-2b, administered as 12 biweekly injections, has also been used as an ILI agent in PD. It has been shown to provide curvature reduction (mean curvature reduction 9° to 14°), significantly reduced plaque size/density, and pain reduction in

placebo-controlled and retrospective trials. Compared to calcium channel blockers, IFN α-2b does have a more robust side effect profile. In addition to ecchymosis, it can also cause significant swelling, inflammation, and possible flu-like symptoms. These minor side effects typically respond well to nonsteroidal anti-inflammatory agents[47,48].

The most notable PD breakthrough in recent years is ILI therapy with collagenase clostridium histolyticum (CCH) which became the first pharmacologic agent to obtain Food and Drug Administration approval for the treatment of PD. It is approved for use in PD patients with minimally-calcified palpable plaque and dorsal or dorsolateral curvature >30° and <90°[49]. CCH is produced by the bacteria *C. histolyticum* and has the ability to induce fibroblast apoptosis and degrade type I and type II collagen (but does not break down type IV fibrillar collagen found in blood vessels and nervous tissue)[50.51]. This approach makes sense clinically because CCH acts as a chemical knife to lyse collagen, which is the main component of Peyronie's plaque. The Investigation for Maximal Peyronie's Efficacy and Safety Studies (IMPRESS) I (417 patients) and II (415 patients) randomized patients to a 4-6 week cycles of CCH vs placebo (saline) injections. Patients enrolled in these trials had palpable plaque with a baseline mean curvature of 50.5°. Patients were excluded if they had previous penile surgery, deformity <30° or >90°, extensively calcified plaque, ventral curvature, poor erectile function, or plaque related pain. At 52 week follow up, penile curvature decreased 34% (50.1° to 33.1°) in the CCH group compared to an 18% decrease (49.3° to 40.0°) in the placebo group. CCH also resulted in significant improvements in Peyronie's Disease Questionnaire scores, a validated objective measurement tool of the psychological effects and bothersomeness of PD[52,53]. Minor adverse events (ecchymosis, swelling,

pain) are common, occurring in 84.2% of patients. Most (79%) adverse events resolved without intervention. Six serious adverse events were reported: 3 corporeal ruptures, 3 severe penile hematomas[34].

In recent years, other injectable agents have been subject to early investigation for use in PD patients. Romano et al recently published a trial of 164 PD patients with acute phase PD with penile plaque volume <1cm randomized to 30 injections of hyaluronic acid vs placebo over a 6 month period. At 12 months of follow up, patients treated with hyaluronic acid had significant reduction in plaque size (-93.7%) and modest improvements in penile curvature (-9.01^0)[54]. Another injectable therapy, adipose-derived stem cells (ADSCs), may prove to be a novel autologous agent to prevent the progression of PD fibrosis. In a rat model of acute-phase PD fibrosis (induced by injection of TGF-β), subsequent injection of ADSCs seems to prevent the development of penile plaque formation and also results in improved erectile function[55,56]. In a small prospective study of five PD patients, intralesional injection of placental matrix-derived mesenchymal stem cells resulted in significant plaque reduction at 3 months[57].

3. Extracorporal Shockwave Therapy and Radiation Therapy:

Theoretically, extracorporal shockwave therapy (ESWT) has been purported to cause direct damage to penile plaque while also inducing an inflammatory cascade with macrophage removal of plaque components, ultimately resulting in remodeling of the penile plaque. Although ESWT has been shown to reduce pain and provide modest improvement in sexual function in small controlled trials, it is ineffective at reducing penile curvature or plaque size[58,59]. Although ESWT seems to be effective in regard to

pain reduction, it is important to remember that PD related pain usually resolves spontaneously with time, regardless of treatment. Side effects include local petechiae and ecchymoses.

In vitro studies have suggested that low dose radiation therapy has anti-inflammatory effects that could theoretically inhibit or reverse the effects of PD. Unfortunately, in PD patients, radiation therapy has demonstrated no benefit when compared to placebo[60]. Most experts agree that radiation should be avoided in PD patients due to lack of proven efficacy and potential side effects including risk of malignant change and erectile dysfunction (ED)[11,61].

4. Mechanical Therapies

Penile traction therapy (PTT) is well supported as a viable nonsurgical first line therapy for select PD patients. In vitro, PTT decreases alpha-smooth muscle actin and increases matrix metalloproteinase activity within the treated tissue. Ultimately mechanotransduction via tissue traction leads to collagen degradation and scar remodeling, as evidenced by the reorientation of collagen fibrils in line with the direction of applied force[62-64]. The initial evaluation of PTT in 10 patients resulted in average decreased curvature by 33% (10-45 degree improvement). PTT also resulted in increased stretched penile length (range 0.5-2.0cm) and increased girth (range 0.5-1.0 cm)[65]. PTT appears to be most efficacious when used in the acute phase of PD. Recently, Martinez-Salamanca and colleagues prospectively evaluated 55 acute phase PD patients treated with PTT for six months and compared them to 44 acute phase PD patients with no treatment. Traction therapy resulted in average 20 degree decrease in

curvature (33^0 to 13^0), while the untreated patients had 19^0 worsening in curvature. PTT was also found to reduce plaque volume by 39%. After 6 months, 80% of patients treated with PTT were able to have penetrative sexual activity (compared to only 15% in the control group)[66]. Patients with stabilized disease and calcified plaque appear to be less likely to respond favorably to PTT[67]. PTT is an underutilized nonsurgical treatment option for motivated patients with early-stage PD, especially for men who are concerned about penile length and girth preservation. PTT can be employed during the acute and chronic phases of PD and as a combination therapy with other medical and surgical treatment options. The key to successful PTT is duration of therapy. Patients who use the device at least three hours per day have the best chance of a positive response with respect to length, girth, and curvature[68].

Mechanical straightening via vacuum therapy has also been described in a single non-controlled study of 31 PD patients who used vacuum therapy for 10 minutes BID for 12 weeks. A majority (21 of 31) patients had reduction in curvature (range 5^0 to 25^0)[69]. Potential side effects of vacuum therapy include urethral bleeding, penile bruising, and skin necrosis[70].

5. Combination Therapies

Clearly, a variety of therapies have been trialed in PD patients with variable results in their individual ability to reduce deformity, improve sexual function, reduce pain, and prevent length loss. While no single oral agent has shown significant reproducible benefit as monotherapy, the authors feel that oral agents may prove to have synergistic effects when used in combination with injectable and/or mechanical therapies.

Currently, data in support of combination therapies is limited. When combining verapamil iontophoresis with or without oral antioxidants, Paulis et al recently reported that patients treated with combination therapy had greater plaque size reduction (-30.8% vs -18.0%) and were more likely to have reduction of penile curvature (85% vs 52.5%)[71]. PTT has also gained support as a beneficial component of combination therapy, especially in men concerned about penile length preservation. In 39 men with PD, combination therapy of ILI verapamil, PTT, oral pentoxyfilline, and oral L-argininine resulted in significant reduction in penile curvature (from mean 44.4^0 to 33.4^0) after 24 weeks with mean increase in stretched penile length of 0.3cm. Men not utilizing traction lost 0.7cm of length, on average[68].

C. Surgical Therapies

1. Surgical Indications:

Surgery remains the gold standard for patients with severe PD who have failed conservative therapy and desire resolution of deformity and improvement in their ability to have penetrative intercourse. Appropriate candidates for surgery have compromised sexual function, extensive plaque calcification, and/or desire reliable and efficient correction of deformity. Prior to surgery, it is recommended that patients have stable PD (defined as one year from PD onset with at least six months of stable deformity)[11]. As every patient with PD has unique individual characteristics of the disease, there is no single standard surgical approach to adequately address PD. The authors adhere to the surgical algorithm presented in Table 2[72]. Prior to any surgical intervention for PD, patients should be counseled on the possibility of penile length loss, persistent/recurrent

deformity, penile sensory changes, and worsening erectile function. The goal of any intervention should be to render the penis functionally straight, with residual curvature of less than 20^{0}[11]. For men with PD and baseline ED refractory to oral PDE5-i therapy, placement of a penile prosthesis with straightening maneuvers is recommended.

2. Tunica Albuginea Plication (Tunica Shortening Procedures):

A number of simple and effective penile plication techniques have been described that result in durable straightening with sustained rigidity. The first widely accepted tunica albuginea plication (TAP) technique was the Nesbit procedure, which utilizes an elliptical excision and subsequent closure of the tunica albuginea contralateral to the area of greatest curvature. Multiple variations of this technique have evolved, including the Yachia procedure, which corrects dorsal curvature by transverse closure of a short ventral vertical incision contralateral the point of maximum curvature[73]. Imbricating procedures, popularized by Essed and Schroeder, allow for tunical plication without incision. Non-absorbable sutures with buried knots are used to shorten the tunica contralateral to the area of curvature[74]. Others have described imbricating rows and via a more elaborate 16-dot or 24-dot plication with Lembert-type suturing[75-77]. The authors prefer to utilize a modification of the TAP technique first described by Baskin and Duckett. Parallel (1-1.5cm) partial thickness transverse incisions (separated by 0.4-1.0cm) are made in the outer layer of the tunica albuginea contralateral to the area of greatest curvature. The intervening longitudinal fibers of the tunica are excised to reduce the bulk of the plicated tissue and the resulting edges are approximated with a central, inverting vertical mattress permanent suture. Further support is provided by

adjacent, absorbable Lembert sutures. The underlying circular fibers are left intact[78,79].

The main disadvantages of all plication procedures are penile shortening and failure to correct hourglass deformity. The amount of penile shortening after TAP is proportional to the degree of curvature requiring correction; men with ventral curvature of greater than 60^0 have the greatest potential loss of length[80]. After TAP, noticeable penile narrowing or indentation has been reported in up to 17% of patients. Other complications include ED (0-38%), decreased penile sensation (4-21%), hematoma (<9%), and urethral injury (<2%). Furthermore, permanent suture can cause pain and penile granulomas. The current trend in plication repair is to limit or eliminate use of permanent suture[11,81,82].

3. Tunica Lengthening Procedures (Plaque Incision or Partial Excision and Grafting)

PD patients with more severe disease (dorsal curvature $>60^0$, hourglass deformity, penile hinging, and/or extensive plaque calcification) are candidates for plaque incision and grafting (PIG) or partial plaque excision and grafting (PEG)[72,83]. To qualify for a grafting procedure, it is critical that patients have good preoperative erectile function (adequate rigidity for penetrative sex with or without use of PDE5-i's) preoperatively[84,85]. Compared to TAP, grafting procedures have higher rates of postoperative ED, likely due to disruption of the tunica albuginea and underlying corporal tissue. In the largest contemporary series of grafting procedures, rates of postoperative ED range from 20-32%[86-89].

The main advantages of grafting procedures are the ability to correct severe penile curvature and narrowing with one procedure, while also re-establishing a normal caliber shaft and potentially recovering penile length. Based on published reports with five year follow up, grafting procedures result in satisfactory straightening in 74-100% of patients[90-92]. Plaque incision and grafting utilizes modified-H or double-Y incisions of the dorsal plaque near the area of maximum curvature, which allows the fibrotic tunic to expand while minimizing exposure to underlying cavernosa tissue. A graft is then placed within the space created by the incision[93].

Some experts have proposed strict adherence to geometric principles during grafting procedures[94]. A reproducible tridimensional penile model simulating PD curvature was recently created and application of common PIG techniques were all found to be susceptible to mechanical or geometric distortion due to imprecise wound edges that do not match up well with rectangular grafts[95]. To avoid this, the authors prefer to use partial plaque excision and grafting (PEG), especially in cases involving calcified plaque or severe indentation. After careful elevation of the neurovascular bundle, a rectangular excision of tunic involving the dorsal plaque in excised. The corners of this defect are darted radially to ensure resolution of narrowing in this area[96]. In cases involving severe Peyronie's plaque calcification that cannot be excised with a blade, a bone cutting device may be needed to divide the calcified plaque before subsequent grafting[97].

In addition to correcting curvature, a recent advancement in PEG technique by Egydio et al utilizes geometric principals with circular and longitudinal grafting, resulting in successful length and girth restoration. Due to heightened risks for postoperative ED, these techniques should be reserved for men with severe shortening who agree to have

a penile prosthesis implanted to ensure adequate postoperative erectile function[98]. For both PIG and PEG, a variety of autologous grafts have been used, including dermis, fat, tunica vaginalis, dura mater, temporalis fascia, saphenous vein, corporal crura, and buccal mucosa[81,99-105]. Most autologous grafts are no longer used due to extended operative time required for harvesting, risk of infection, and potential for contraction. More recently, commercially produced allografts and xenografts have become available, including Tutoplast™ (Coloplast US, Minneapolis, MN) processed human and bovine pericardium, and porcine small intestinal submucosa (SIS) grafts (Surgisis ES, Cook Urological, Spencer, IN). Pericardial grafts are thin, durable, do not contract, and respond well to suturing[106]. SIS grafts are also widely used, but there have been reports of significant graft contraction (resulting in recurrent curvature) and infection (5%)[88,107]. To help reduce the risk of erectile dysfunction postoperatively, penile rehabilitation is critical and involves routine use of massage/stretch therapy and PDE5-i's, which can help increase nocturnal vasodilation and return of erectile function[108]. Postoperative PTT for three months is strongly recommended to prevent length loss and help guide straight healing of the penis. With diligent use, PTT can result in enhanced penile length (>1 additional cm) after PEG[109].

4. Penile Prosthesis with Straightening Maneuvers

Inflatable penile prosthesis (IPP) is recommended for all men with PD and ED refractory to medical therapy. Upon placement of an inflatable penile prosthesis, curvature is often corrected by inflation of the device. After the device is inflated, additional straightening techniques can be performed if necessary. Careful, gradual manual modeling can be

performed to induce further straightening with the device inflated. Among experienced surgeons, IPP with manual modeling provides successful straightening over 79% of the time[110-113]. If residual curvature is still >30^0, plaque incision with (if defect >2cm) or without grafting may be necessary[114]. The most common adverse effect of IPP placement in PD patients is perceived length loss[115,116]. In men motivated to retain length, traction therapy can be initiated prior to surgery. When used 3 hours per day for at least 3 months, the majority of PD patients will demonstrate length gain (range 0.5cm-2.0cm) prior to IPP placement[117]. Although technically demanding, circumferential plaque incision and grafting or a double dorsal-ventral patch graft "sliding technique" at the time of IPP placement can result in substantial length restoration[98, 116].

Conclusion

The number of patients presenting to urologists with PD is on the rise. Although a myriad of treatment options have been proposed for PD, most studies are limited by study design and sample size. Although numerous oral agents have been subjected to small randomized trials, no single oral agent has demonstrated significant or reproducible benefit as monotherapy for PD. Better results, especially in regard to disease stabilization and curvature reduction, have been seen with ILI verapamil, ILI interferon-α2b, and the recent addition of intralesional CCH. Further experience with CCH will allow better discrimination as to the optimum candidates. Clearly, it appears that the goal of non-surgical treatment at a minimum should be to prevent progression of deformity during the acute phase. Non-surgical treatment options including oral,

injectable, mechanical, and combination therapies should be aimed at reducing deformity to improve sexual function and reduce bother caused by fibrosis. At this time it is the opinion of the authors that combination therapies utilizing oral therapies, intralesional injections, and mechanical traction may offer the best opportunity for meaningful results by creating a synergy between the chemical effects of pharmacotherapy with the mechanical effects of external forces on the penis.

If surgery is warranted, the goal should be to decrease curvature and correct deformity so that penetrative sexual activity is feasible, without compromising erectile function or causing further length loss. Pre-operatively, patients must be aware of possible penile shortening associated with these procedures, as well as the risk of ED and importance of postprocedural rehabilitation. In men motivated for length recovery, PTT (used either pre or post-operatively) remains a viable, albeit labor intensive, option. In men with PD and ED refractory to medical therapy, placement of a penile prosthesis with manual modeling and additional straightening (plaque incision/excision +/- grafting) if necessary represents the best approach to optimize cosmetic and functional outcomes.

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Table 1. Oral Therapies Trialed in Peyronie's Disease

Oral Therapy	Mechanism of Action	Available Evidence	Annotations and Side Effects
Potaba	Decreases fibrosis and inhibits collagen deposition by decreasing serotonin levels, increasing monoamine oxidase activity, and limiting fibroblast glycosaminoglycan secretion[15]	One RCT: No improvement in curvature[16]	Expensive and difficult drug administration (24 tablets daily). *Significant side effect profile: decreased appetite, nausea, rash, fever, hypoglycemia, acute hepatitis
Vitamin E	Inactivates free radicals, limits oxidative stress[17]	Multiple placebo controlled trials as monotherapy: no significant improvement in plaque size, curvature, pain, or sexual function compared to placebo[11,18,19]	Potential side effects: cerebrovascular events, nausea, vomiting, diarrhea, headache, dizziness
Tamoxifen	Selective estrogen receptor modulator; at high concentrations tamoxifen increases TGF-β , providing negative feedback for inflammatory cascade[20]	One small RCT: no significant improvement in penile deformity, plaque size, or pain compared to placebo[21]	Potential Side Effects: hot flashes, erectile dysfunction, GI distress, alopecia, retinopathy, thromboembolism, pancytopenia
Procarbazine	Alkylating chemotherapeutic agent	Small trials (1970's): No evidence of objective benefit.[22]	Chemotherapeutic agent. *Significant Side Effects: vytotoxicity, myelosuppression, hepatotoxicity, fatigue, CNS disturbance, GI distress
Colchicine	Depolymerizes tubulin, inhibits cell mitosis, prevents leukocyte adhesion	One RCT: no improvement in curvature or plaque size	*Significant side effects reported: abdominal pain, nausea, diarrhea,

	and transcellular collagen transport; may stimulate collagenase production[23,24]	compared to placebo[25]	aplastic anemia
Carnitine	Mitochondrial fatty acid transporter with anti-oxidant properties; inhibits acetyl coenzyme-A, increases mitochonrdrial respiration, decreases free radicals[26]	One RCT: no significant improvement in curvature, plaque size, or pain compared to placebo[27]	Possible side effects: diarrhea, abdominal bloating,nausea, vomiting, seizure,hypotension
Pentoxifylline	Nonspecific phosphodiesterase inhibitor; prevents fibroblast activity and collagen deposition; increases fibrinolytic activity[14]	One single center RCT in 2010 showed possible benefit[28]. (However, this study was later retracted).	Possible side effects: fatigue, nausea, vomiting, dyspepsia, flushing, dizziness, headache
Omega-3 Fatty Acids	Anti-inflammatory, limits deleterious effects of eicosanoids[29]	One single center RCT: no improvement in curvature, pain, or erectile function compared to placebo[29]	Side effects: minor GI distress, fishy breath
Coenzyme Q10	Fat-soluble quinine, anti-oxidant and anti-inflammatory properties [30]	One single center RCT in chronic PD patients: improvement in curvature, erectile function, and pain compared to placebo at 24 weeks[30]	Further evaluation necessary. Possible side effects: diarrhea, loss of appetite, nausea, trouble sleeping
PDE-5 Inhibitors	Inhibits collagen synthesis, induces fibroblast apoptosis by increasing cGMP and nitric oxide[14]	One small randomized trial (39 patients): modest reduction in plaque size and significant improvement in erectile	Safe and effective for PD patients with ED No large scale RCTs to confirm improvement in curvature.

		function compared to Vitamin E[31]	Side effects: headaches, dizzyness, flushing, heartburn, blue vision, myalgias

Table 2: Algorithm for Surgical Management of Peyronie's Disease

Surgical Procedure	Indications
Tunica Albuginia Plication (TAP)	*Stable deformity *Subjective or objective full erectile capacity *Simple curvature less than 60 ^{0} *No hourglass deformity or hinge effect
Partial Excision and Grafting (PEG)	*Stable deformity *Subjective or objective full erectile capacity *Complex or bidimensional curvature *Curvature greater than 60 ^{0} *Significant hourglass deformity or hinge effect
Penile Prosthesis Placement (IPP)	*Stable deformity *Suboptimal erectile capacity