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Brief review

Peyronie's disease: epidemiology, diagnosis, and management

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Abstract

Objective:
Peyronie's disease (PD) is a progressive fibrotic disorder of the penis that is characterized by formation of collagen plaques on the tunica albuginea of the penis that may result in penile deformity, pain (typically early in the disease course), and often occurs in conjunction with erectile dysfunction. This review's purpose is to raise awareness of PD among primary care physicians, who are likely to provide the initial diagnosis and information to patients.

Methods:
PubMed was searched for articles related to epidemiology, diagnosis, and management of PD. Reference lists of relevant articles were also examined for further pertinent research. Following the goals of this review, references were selected based on their appropriateness for a primary care audience.

Results:
The symptoms of PD may physically limit intercourse and impose a severe physical and psychological burden. The course of PD includes an early 'inflammatory' phase that may last 1–18 months and a subsequent 'stable' phase. In the early phase, patients may experience penile pain as the tunical plaque develops. During the stable phase, the plaque becomes more organized, penile curvature stabilizes, and the pain usually subsides. Currently, there are no US Food and Drug Administration approved therapies that have shown significant efficacy for PD. Nonsurgical treatment options are often used to manage PD with variable success. Most studies of nonsurgical management of PD are small, poorly controlled, and include patients in variable disease stages. Surgical treatment of PD is reserved for stable patients with erectile dysfunction and penile deformity that impairs sexual function.

Conclusion:
PD is frequently undiagnosed. Even when PD is correctly identified, choice of treatment is problematic, based on the limited currently available clinical data demonstrating clinical benefits associated with treatment. Newer medications in clinical testing seem to offer some potential benefit for men with PD, though further research is necessary.

Introduction

Peyronie's disease (PD) is a wound healing disorder within the penis characterized by formation of a fibrous inelastic plaque, predominantly of collagen, on the tunica albuginea, the fibrous sheath surrounding the corpora cavernosa of the penis. The formation of fibrotic plaques results in penile deformities during erection including curvature, shortening, narrowing (hourglass), and bending (hinge effect) (Figure 1)[1–3]. The degree to which PD limits sexual performance varies depending on the angle and orientation of the penile curvature[4]. Patients with mild curvature may feel slight discomfort during penetration, while patients with more severe curvature may be incapable of intercourse. Interestingly, some

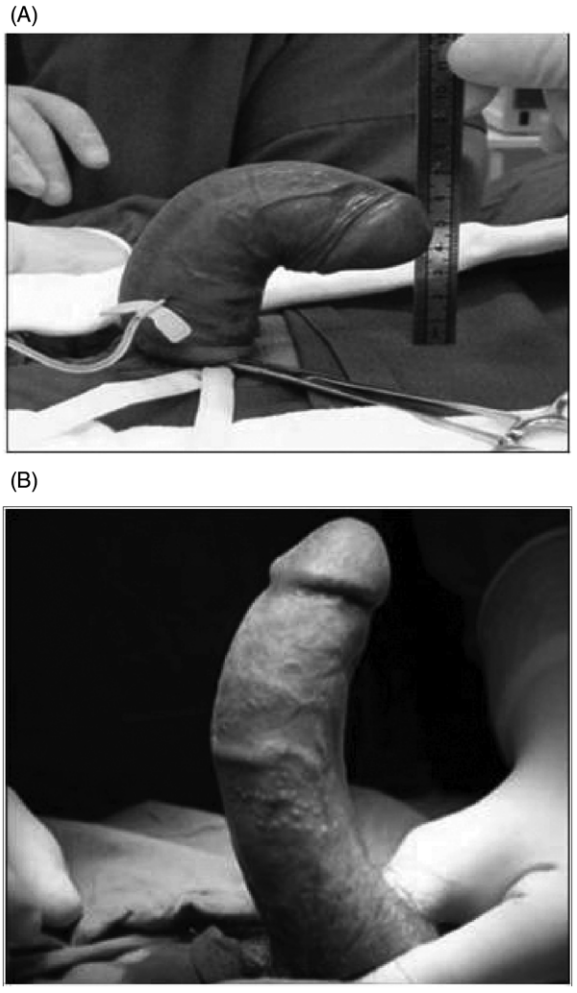

Figure 1. Photographic examples of deformities associated with PD (dorsal curvature, A and B). Images courtesy of Dr. Andrew McCullough, Albany Medical School. Used with permission.

evidence suggests that the degree of curvature deformity does not directly correlate with the severity of the psychosocial bother of the disease. Men with lesser degrees of curvature may be as bothered as men with more severe deformities. The symptoms of PD are frequently accompanied by varying degrees of erectile dysfunction (ED)[2,5]. Pain may or may not be correlated with the development of penile curvature.

The prevalence of PD is often underestimated. A survey of 152 primary care physicians (PCPs) and 98 urologists found that both urologists and, to a greater extent, PCPs underestimate the prevalence of PD and the rate of ED in patients with PD and overestimate the rate of spontaneous resolution[6]. In addition, 44% of PCPs and 17% of urologists reported that they do not examine the penis as part of a routine physical, which the authors note is a missed opportunity to allow a patient to bring up any concerns he might have. Among those who did provide treatment for PD, both groups were likely to prescribe vitamin E as first-line treatment, although its efficacy is unproven (see discussion below), and were unlikely to recommend surgical correction. The authors conclude that all of these factors suggest underdiagnosis and undertreatment of PD that can be corrected by raising awareness among healthcare providers. Underdiagnosis is of particular concern as it can delay effective treatment[7].

The purpose of this review is to raise awareness of Peyronie's disease among PCPs, who are likely to provide the initial diagnosis and information to patients. A PCP may be the first physician consulted by a patient; it is particularly important that these physicians are able to provide early recognition of PD and direct the patient to appropriate follow-up and treatment.

Presentation and diagnosis of PD

Most patients with PD present within 6 months of symptom onset[8]. The most common presenting symptoms of PD are penile deformity (predominantly curvature), penile pain, and penile plaque, in that order[8]. Patients typically have either a well defined plaque or an area of hardening on the penis that is palpable on physical examination, although patients may be unaware of it[1]. The plaque typically becomes harder with disease progression and may calcify[8]. Patients with type 2 diabetes mellitus (DM) and ED should also be screened as potential PD patients. In a prospective survey of all male patients ($n = 1133$) with a diagnosis of type 2 DM treated at a hospital in Saudi Arabia, 85.6% had varying degrees of ED, and 8.1% had PD[9].

The diagnosis of PD is based on medical history, symptomatology, and identification of penile plaque by palpation. Imaging, particularly ultrasonography, can also be used to identify the site and characteristics of the plaque[10]. Extensive plaque calcification is a predictor of poor response to minimally invasive therapies and thus may be an indicator for surgical treatment[1]. Because they are often the first physician consulted by a patient[7], PCPs are important for early recognition of PD. Final diagnosis and treatment of PD is typically performed by a urologist.

Burden of disease

PD can cause significant psychological bother/distress and potentially strain sexual relationships[11]. Anxiety and stress manifest in a variety of ways. In a survey of 92 men with diagnosed PD, 48% were classified as clinically depressed based on their scores on the Center for Epidemiological Studies Depression scale[12]. In an analysis of the prevalence of depression as a function of time since diagnosis, the percentage of PD patients with depression did not change significantly for periods as long as >18 months

following diagnosis, suggesting lack of mental adjustment to the diagnosis of PD[12]. Similarly, in a subset of patients who were assessed for depression at baseline and after 18 months, the percentage of patients with severe depression was not statistically different (21% vs. 23%, respectively)[12]. Given the high initial rate of depression, the authors concluded that all men with PD should be screened for mental illness[12].

In addition to overt mental illness, men with PD also experience problems with psychosocial and sexual function. In interviews, patients with PD indicated that problems with functioning typically fall into one or more of four domains: (1) physical appearance and self-image; (2) sexual function and performance; (3) PD-related pain and discomfort; and (4) social stigmatization and isolation[13]. While men with PD varied in the type and intensity of their subjective reactions to this condition, the major themes and patterns of response were consistent across groups[13]. A questionnaire survey of men with PD also revealed a high prevalence of emotional and relationship problems[14].

Epidemiology

Estimates of the prevalence of PD are limited and highly variable. In the general population, reported prevalence of PD has ranged from 8.9% in men undergoing screening for prostate cancer[15] to 0.39% in patients in Rochester, Minnesota between 1950 and 1984[16]. The highest reported prevalence of PD is 20.3% in patients with DM and ED[17]. The prevalence of PD in the general population may be underreported due to the reluctance of patients to visit their physician with this embarrassing condition[7]. More recently, a web-based survey of a large ($n = 11,420$) probability-based panel of research subjects representative of the full US population estimated the prevalence of PD to range from 0.5% (the percentage of surveyed subjects with PD diagnosis) to 13% (percentage with diagnosis, treatment, or penile symptoms of PD). The management of participants who sought treatment for penile symptoms ($n = 128$) was inadequate; 74% did not receive treatment during their first physician visit, and 92% were not diagnosed with PD[7].

A number of clinical and demographic features have been independently associated with PD after multivariate analysis. Patients with PD are more likely to be white[18] and older[15]. ED was an independent predictor of PD in one study[15] but was not significantly correlated with PD in another[18]. Younger patients with PD are more likely to have DM and multiple plaques than patients with PD older than 40 years of age[19]. Finally, some studies support an increased risk of Peyronie's disease for men with sexual dysfunction following radical prostatectomy, with additional risk in men who are younger and/or white[20–22].

Course of disease

The earliest presenting symptom of PD is typically penile curvature[23]. The early phase of PD (up to 18 months) is also marked by formation of a palpable penile plaque with or without penile pain. During the late phase of PD, the pain decreases and the penile plaque becomes more organized and sometimes calcified[23]. During an 18 month follow-up study of 246 patients with early-stage PD, 12% of patients had improved curvature of the penis, 40% were unchanged, and 48% experienced worsening curvature. Pain improved during follow-up and resolved in 89% of patients[23]. In a cohort of 110 patients with early-stage PD who were followed for 5 years, stabilization of disease was more common in patients who were older (>50 years) at inclusion in the study than in patients who were <50 years old. Patients with PD and DM were more likely to experience progression of PD than patients without DM[3].

In a more direct study of the effects of DM on progression of PD, 59 patients with PD and DM but no other comorbidities were followed for 12 years and compared with 109 men with PD and no known risk factors. Each patient underwent baseline penile duplex Doppler ultrasonography to evaluate stimulated penile blood flow[24]. Patients with DM and PD had a greater mean degree of penile deformation and rate of severe penile curvature (>60°). The percentage of patients with ED was also higher in patients with PD and DM compared to PD alone[24]. The association of DM with more severe PD and increased prevalence of ED may be related to the poorer values of peak systolic velocity and higher rates of arterial insufficiency seen in these patients compared to patients with PD but no DM[24].

Etiology

The etiology of PD is not completely understood. One of the most commonly cited potential causes of PD is repeated mechanical stress and microvascular trauma of the penis resulting from excessive bending or single blunt trauma to the erect penis with resultant bleeding into the subtunical spaces and tissue damage. Fibrin deposits in the injured tissue may initiate an inflammatory wound healing response with resultant recruitment of macrophages, neutrophils, and fibroblasts[25]. Direct proof of this hypothesis is limited, and two follow-up studies of subjects treated for penile fracture have failed to note any correlation between penile damage and subsequent PD[26,27]. Transforming growth factor-β, a factor released during the wound healing process, stimulates proliferation of and collagen deposition by fibroblasts and myofibroblasts. The excessive collagen deposition leads to plaque formation[25].

There may also be a genetic component to the etiology of PD. Gene expression patterns in patients with PD are similar to those in patients with Dupuytren's disease (DD), a proliferative connective tissue disorder of the hand that causes the fingers to bend inward toward the palm. This observation suggests that PD and DD share common pathophysiologic features[28]. There also appears to be a close clinical connection between PD and DD. In a cross-sectional analysis of factors associated with PD, patients with PD ($n = 83$) had a significantly higher rate of coexisting DD than age-matched controls (6% vs. 0%; $p = 0.001$)[18]. In a larger cohort of Dutch patients with diagnosed PD, 22.1% also had DD[29].

Treatment

Nonsurgical treatment of PD is typically used for men with early-phase, unstable disease, as well as those not psychologically ready for or interested in surgery[1,2]. Development of effective nonsurgical treatments has been complicated by a lack of clear understanding of the etiology of the disease[2]. As a result, multiple treatment options have been investigated, although the quality of these studies is sometimes variable. Published reports of the pharmacological treatment of PD typically have small patient populations, are not well controlled, and include subjects in varying degrees of disease progression. Studies have frequently focused on pain abatement and plaque reduction as end points of treatment. In contrast, the authors of a recent evidence-based guideline for the management of PD suggest that reduction of penile deformity should be considered the most critical outcome measure[1]. As this paper focuses on the recognition and diagnosis of PD, please see recent reviews by Paulis and Brancato[30], Larsen and Levine[31], and Serefoglu and Hellstrom[32] for more detailed information about treatment options for PD.

Oral agents

Several oral nonsurgical treatments for PD have demonstrated some degree of efficacy in small clinical trials (Table 1)[1,2,33–37]. However, because these are individual studies presented for each agent, further studies will be necessary to confirm any of the results. In addition, several oral agents have demonstrated no benefit as monotherapy for reducing the deformity of PD. Mixed results have been found for potassium aminobenzoate (Potaba®) and tamoxifen[1,2].

As mentioned earlier, vitamin E is one of the most commonly used treatments for PD. It is a potent antioxidant that is thought to reduce collagen deposits[38]. Vitamin E has been considered ineffective[1,2] based on studies that did not find significant benefits of vitamin E treatment[39,40], though a recent study found a benefit of vitamin E on erectile function[38].

Based on its ability to inhibit collagen secretion from fibroblasts, colchicine has been examined as monotherapy for PD[41]. Although colchicine did not show efficacy as monotherapy in that study, the combination of colchicine and vitamin E was shown to significantly improve penile curvature and plaque size in a single-blind study[33].

Phosphodiesterase (PDE) inhibitors such as pentoxifylline and tadalafil have shown antifibrotic effects in preclinical studies, potentially due to their ability to increase cyclic guanosine monophosphate (cGMP) levels by inhibiting the breakdown of cGMP to 5′-GMP[34,42]. In one study, pentoxifylline sustained release demonstrated clinically modest but statistically significant benefits in terms of reduction of penile curvature and plaque volume[34], and in a retrospective cohort study, pentoxifylline treatment was associated with stabilization or reduction of disease[36].

Oral tadalafil treatment has been studied in patients with PD and ED of at least 12 months' duration[37]. All patients in the study received extracorporeal shock wave therapy (ESWT); half were randomized to also receive tadalafil (5 mg). At both 12 and 24 months posttherapy, improvements were seen in both groups in measures of mean curvature degree, mean plaque size, presence of painful erections, erectile function, and quality of life. Significantly greater improvements were seen in the ESWT + tadalafil group compared with ESWT alone in erectile function and quality of life.

An early study of oral acetyl-L-carnitine found efficacy in the treatment of PD[43]. A larger study of propionyl-L-carnitine with verapamil also found significant reductions in penile curvature and plaque size[35]. However, a randomized study did not find significant effects of propionyl-L-carnitine alone or in combination with placebo[39].

Injectable agents

Several products that are delivered as injections into the penile plaque have been tested as treatments for PD. Treatment with injectable agents is typically performed by a specialist. Verapamil, a calcium antagonist, has been used to treat PD based on its ability to alter fibroblast production of extracellular matrix macromolecules and collagenases[44]. In a nonrandomized trial, 156 men with PD of 18 months' mean duration were given injections of 10 mg of verapamil into the penile plaque every 2 weeks for 24 weeks. Of the 140 patients who completed treatment, 121 were evaluated with a second duplex ultrasound and 73/121 (60%) had an objectively measured decrease in curvature, while 92 of 130 patients reporting on sexual function (71%) reported improved sexual function ($p < 0.0001$)[44]. In a subsequent randomized,

Table 1. Oral agents with demonstrated benefits in the treatment of PD.

Agent	Rationale	Patients	Design	Outcomes
Vitamin E (600 mg/day) plus colchicine (1 mg/12 hrs) for 6 months; NSAIDs used as active control (Prieto Castro *et al.*, 2003)[33]	Colchicine was originally proposed for use in the early stages of PD because of its ability to activate collagenases and to decrease collagen synthesis	Early PD (<6 mo duration); no ED; penile curvature <30°; $n = 23$	R, DB, active control (ibuprofen 400 mg/day). Plaque size reported as a length (cm) rather than an area measurement	Higher percentage of patients in the treatment group vs. the active control group showed improvement in penile curvature (11% vs. 4%, $p = 0.01$) and improvement in mean penile plaque size (−0.26 cm vs. +0.13 cm, $p < 0.001$)
Pentoxifylline (PDE inhibitor) 400 mg bid or placebo for 6 mo (Safarinejad *et al.*, 2010)[34]	Pentoxifylline has been tested in PD because of its known ability to downregulate inflammation and increase fibrinolytic activity	Early chronic PD (>12 mo duration); $n = 228$	R, DB, PC. Penile curvature broken down into ventral, dorsal, and lateral	Significant change with active treatment vs. placebo in mean penile curvature (ventral: −40° vs. +26.9°, $p = 0.001$; dorsal: −22.2° vs. +31.4°, $p = 0.01$; lateral: −20° vs. +22.2°, $p = 0.01$); and mean penile plaque size (−28.6 mm^2 vs. +42.9 mm^2, $p = 0.001$); active treatment halted disease progression in 52% of pentoxifylline patients
Pentoxifylline, generally at 400 mg tid vs. no intervention or vitamin E monotherapy (Smith *et al.*, 2011)[36]	Pentoxifylline was examined due to its ability to decrease inflammation and calcification and prevent fibrosis	PD and sonographic evidence of penile calcification; $n = 71$	Retrospective cohort study	Significantly greater likelihood of: improvement in calcifications (69.4% vs. 33.3%, $p = 0.03$); stabilization (no change) or improvement in calcium burden (91.9% vs. 44.4%, $p < 0.001$); and self-reported sense of clinical improvement (78.3% vs. 25.0%, $p = 0.002$) with pentoxifylline treatment vs. no pentoxifylline
Oral propionyl-L-carnitine (PLC; 2 g/day for 3 mo) plus verapamil intraplaque infiltration (10 mg/week for 10 weeks), or verapamil plus oral tamoxifen (40 mg/day) for 3 mo (Cavallini *et al.*, 2002)[35]	PLC has been used to treat PD based on its ability to downregulate inflammation	Patients with early ED excluded; $n = 60$	R, DB	PLC–verapamil combination resulted in a significantly greater improvement in penile curvature (−11.8° vs. −1.9°, $p < 0.01$) and plaque area (−7.6 mm^2 vs. −1.3 mm^2, $p < 0.01$) than the verapamil–tamoxifen combination
Oral tadalafil 5 mg once daily for 4 weeks[37]	Phosphodiesterase (PDE) type 5 inhibitors have shown antifibrotic effects in preclinical studies and both PDE type 5 inhibitors and extracorporeal shock wave therapy (ESWT) have shown efficacy in improving erectile function in patients with PD	Patients with PD and ED of at least 12 months' duration; $n = 100$	Half of patients were randomized to receive ESWT alone and half were randomized to also receive tadalafil (5 mg)	At 12 weeks, significantly greater improvements were seen with ESWT + tadalafil vs. ESWT alone only in erectile function (20.18 vs. 18.48, $p < 0.05$) and quality of life (20.98 vs. 19.46, $p < 0.05$) Similar results were seen at 24 weeks for ESWT + tadalafil vs. ESWT alone (erectile function: 21.48 vs. 18.78, $p < 0.05$; quality of life: 22.48 vs. 21.08, $p < 0.05$)

DB, double-blind; ED, erectile dysfunction; PC, placebo-controlled; PDE, phosphodiesterase; R, randomized.

open-label trial that tested the efficacy of the same dose of verapamil (10 mg) in three progressively more dilute solutions, the most dilute solution (10 mg in 20 mL of saline) was the most effective for treating the symptoms of PD, with no increase in side effects[45]. The effectiveness of the most dilute solution may be related to cracking of the plaques resulting from increased hydrostatic pressure from the larger volume of injectate[45]. The results of one study suggest that the effectiveness of verapamil may be enhanced by testosterone supplementation[46], and another study suggests that transdermal electromotive administration of verapamil is as effective as intralesional injection and may reduce erectile pain to a greater degree[47].

Injection of interferon α-2b into penile plaques has also been tested as a treatment for PD. The proposed utility of interferon α-2b for PD is based on the ability of this agent to decrease the rate of proliferation of fibroblasts derived from PD plaques, decrease the production of extracellular collagen, and increase the collagenase production in vitro[48]. The efficacy and safety of interferon α-2b in PD was tested in a single-blind, placebo-controlled, parallel-group study that enrolled 117 men with PD of at least 1 year's duration. Saline (control) or interferon α-2b (5×10^6 U) were administered biweekly for 12 weeks[48]. Treatment with interferon α-2b resulted in significant improvement in penile curvature ($p < 0.01$), plaque size ($p < 0.001$), and plaque density ($p < 0.05$) compared with controls[48]. However, another small, randomized study ($n = 30$) of interferon α-2b (5×10^6 U) with or without vitamin E in comparison to vitamin E only found no significant changes in penile curvature, plaque size, penile pain, or quality of sexual intercourse[49].

Iloprost, a prostacyclin I2 analogue, was examined as a treatment for PD based on its fibrinolysis-promoting and immunoregulatory properties[50]. In addition to other effects, it is thought to inhibit the expression of collagen type 1. In a small study of patients with PD with stable plaques treated with 200 ng/mL iloprost, 29% (10/32) reported a reduction in penile curvature that was supported by clinician evaluation of the results of at-home photography (AHP), with a clear decrease in pain symptoms during erection. A total of 57% (18/32) of patients reported no clinical efficacy and 14% (4/32) reported a worsening of the disease that was not supported by AHP findings. The authors concluded that further studies, perhaps including higher doses or more frequent injections of iloprost, are warranted.

The use of collagenase produced by the bacterium *Clostridium histolyticum* to disrupt the collagen plaques associated with PD was investigated in two large identical multi-institutional phase 3, double-blind, randomized, placebo-controlled studies (the Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies [IMPRESS] I and II)[51]. Collagenase clostridium histolyticum (CCH) is a purified mix of two collagenases that have demonstrated safety and efficacy in early clinical studies in patients with PD and currently has an indication for treatment of adult patients with Dupuytren's contracture with a palpable cord[52]. A total of 832 patients with PD of at least 1 year in duration and penile curvature of ≥30° were randomized to receive 0.58 mg CCH or placebo, through a maximum of four treatment cycles with two injections per cycle separated by approximately 24–72 hours, with the second injection in each following 24–72 hours later by penile plaque modeling (i.e., stretching of the flaccid penis in a direction opposite that of the curvature following injection)[51].

The primary efficacy endpoints of the study were percentage change in penile curvature deformity and changes in PD symptom bother assessed using the Peyronie's Disease Questionnaire (PDQ) from baseline to week 52. The PDQ is a validated 15-question survey designed to quantify the psychosexual impact of PD[53]. Mean penile curvature at baseline was 50.1 ± 14.4° and 49.3 ± 14° in subjects randomized to CCH and placebo, respectively. Treatment with CCH resulted in significant improvement in percentage change in penile curvature compared with placebo treatment (34.0% vs. 18.2%; $p < 0.0001$)[51]. Significant improvements in the PD symptom bother domain score (determined using the PDQ) for CCH-treated subjects compared with placebo subjects (2.8 ± 3.8 vs. 1.8 ± 3.5; $p = 0.0037$) were also observed. Adverse events were typically mild to moderate and approximately 79.0% (3200/4049) resolved without intervention[51].

Mechanical treatment

A mechanical strategy that involves the use of a vacuum pump has also been investigated for the treatment of PD. The pump applies mechanical stretching to the tunica to lengthen it and straighten the penis. In a small study ($n = 31$), use of a vacuum pump for 12 weeks resulted in significant improvement in mean penile length ($p < 0.029$), angle of curvature ($p < 0.001$), and pain in patients ($p < 0.012$) with mean duration of PD of <1 year[54]. Overall, 21 patients experienced a reduction of curvature, 3 worsened, and 7 remained unchanged.

In a larger study ($n = 74$), all patients were treated with intralesional verapamil injections (IVIs) as well as oral pentoxifylline and L-arginine, and were given the option of adding penile traction therapy (PTT)[55]. The effects of treatment on stretched penile length (SPL), erect penile curvature (EPC), and patient-reported subjective measures were examined. Statistically significant reductions in EPC were observed in both groups. Patients in the group that used PTT in addition to IVI and oral treatments were significantly more likely to gain SPL ($p < 0.001$), with longer durations of PTT use (in hours per day) predicting greater gains in SPL.

Surgical options

Surgical management of PD should be limited to patients with stable disease and is indicated when the curvature of the penis impedes sexual penetration or if there is an associated ED that fails to respond to medical treatment. Surgery may also be appropriate for patients with extensive plaque calcification or for a patient with stable disease who wants a relatively quick result[1]. The three basic types of surgery for PD include penile shortening procedures, tunical lengthening procedures, and penile prosthesis implantation[1,56,57]. The appropriate surgery for each patient is chosen based on criteria that include preoperative ED, preoperative erectile length, magnitude and complexity of penile curvature, and patient and partner expectations[1,56,57]. Further information on surgical treatments is beyond the scope of this review but can be found in a recent review by Segal and Burnett[58].

Conclusions

PD is frequently undiagnosed and there are no US Food and Drug Administration nonsurgical options specifically approved for use in patients with PD. When diagnosing, it is important to differentiate PD from similar symptoms observed with occurrence of ED. Even when PD is correctly identified, choice of treatment is problematic, based on the limited clinical data currently available. Newer medications in clinical testing (e.g., interferon α-2b and CCH) seem to offer some potential benefit for men with PD, and availability of updated results on current clinical studies with these agents will be useful to validate their utility and safety and establish effective treatment protocols. For patients with stable PD and those with intractable ED, surgery may be a viable treatment alternative.

Transparency

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