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MODERN NON-INVASIVE METHODS FOR TREATING PEYRONIE'S DISEASE

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ABSTRACT

Summary: Peyronie's disease (PD) is a common disease in men that can lead to significant penile deformity and pain, erectile dysfunction, and mental health problems. So far, surgical correction with plaque removal offers the greatest likelihood of success during the stable phase of the disease. However, for men in the acute phase of PD or those with a milder deformity who choose to avoid surgery, conservative treatment methods are also available.

New innovative methods are extracorporeal **shock wave therapy (ESWT**) and ultrasound therapy. Intralesional therapy with IFN-α2b, verapamil, and Clostridium histolyticum (CCH) collagenase can significantly reduce penile deviation (PD), but these results may not be clinically significant in men with more severe disease. Iontophoresis (EMDA, electromotive drug administration) of verapamil and cortisone have shown reductions in PD and penile pain.Penile traction therapy offers clinically significant improvement in penile length and curvature. It requires daily therapy lasting several hours. Oral therapies with substances such as L-arginine, L-citrulline, vitamin E and phosphodiesterase inhibitors are most helpful as part of a combination regimen rather than as monotherapy. Regenerative therapies with stem cells and platelet-rich plasma, as well as intralesional therapy with botulinum toxin (Botox) have not yet been well clinically studied and their possible application is currently taking place within the framework of clinical research. The combination of various oral, topical, intralesional therapies, extracorporeal shock wave therapy, ultrasound and traction therapies together with clinical psychosexual therapy if needed could provide a more effective treatment, which in turn could prevent or reduce the need for definitive reconstructive penile surgery.

Materials and methods: For the purposes of the literature review, a systematic search was conducted for articles in German and English on non-invasive treatment methods for Peyronie's disease. The articles were selected according to their relevance to the given topic. The main findings were summarized and presented in tabular form.

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Introduction.

PB is an acquired fibrous disorder of the tunica albuginea of the penis, with a partially understood pathophysiology, which is believed to be a possible result of penile trauma [1], which in turn leads to penile curvature, deformation and shortening, painful erections and **erectile dysfunction (ED)** [2]. An underlying pathophysiological mechanism is thought to be the result of penile mal-healing due to repetitive injury with subsequent extravasation and accumulation of various profibrotic factors, particularly transforming growth factor beta-1 (TGFβ1), fibrin and myofibroblasts between the layers of the tunica albuginea [3,4]. The development of PD is more common in genetically susceptible individuals and in certain high-risk populations such as diabetic men or those with fibrotic disorders, after penile trauma or after treatment for prostate cancer [5]. The formation of fibrous tissue divides the disease and its predominant symptoms into two phases [6]. During the active phase, PB is characterized, in most cases, by the formation of a plaque, deformation of the penis and the appearance of painful erections. These clinical symptoms are followed by the stable phase, which is usually characterized by stabilization of penile deformity and resolution of pain [7]. PD is also an exhausting disease that can lead to mental disorders in affected patients [8]. Known risk factors for the development of PD are diabetes, hypertension, hyperlipidemia, and smoking, which contribute to vascular and neural damage, as well as Dupuytren's disease [9–11]. Treatment of PB is mainly based on timely diagnosis and prompt surgical intervention after stabilization of clinical symptoms. Conservative treatment has a place mainly in patients in the active phase in order to improve pain and prevent the progression of the disease and for patients in the stable phase of the disease who do not wish to undergo surgical intervention [12]. Many oral, intralesional, and topical therapies used in clinical practice show limited efficacy when administered individually. However, it has been suggested that combinations of conservative therapies may contribute to significantly more effective treatment of PD, based on presumed synergistic effects [13]. The requirements for the ideal conservative therapy is that it should be scientifically validated, safe to apply, and at the same time to prevent further progression of the disease, to lead to a reduction of PD and improve sexual function [13]. It has not yet been established in which combination different conservative methods have the greatest effect in improving the disease, during its active or stable phase. [14]. In the framework of this scientific review, we made a systematic review of current therapies, possible combinations between them, their safety and efficacy in the treatment of PB.

Mechanism of action of extracorporeal shock therapy (ESWT) in the treatment of PD (Table 1). The angiogenic properties and mechanical trauma that occur after low-intensity shock wave therapy [15] contribute to the production of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS), which in turn stimulate neovascularization [16]. Shock therapy (ESWT) has also been shown to stimulate the production of local penile progenitor cells as observed in clinical studies in rats, which in turn can be considered as one of the possible mechanisms of action [17]. The exact mechanism of action of shock wave therapy in BP is still not fully understood, although there are 2 main hypotheses. The first hypothesis suggests that the shock waves directly damage the penile plaques, leading to penile tissue remodeling, while the second hypothesis suggests that the heat generated by the shock waves causes an inflammatory reaction that leads to increased macrophage activity and subsequent degradation of the plaque. Available studies with extracorporeal shock therapy (Table 1) have shown a reduction in pain in patients with PD [19–26], a reduction in PD [19–21,25,26], a reduction in plaque [20,21,25] , improving erectile function (EF) [20,21,23,25], lengthening the penis [21], improving quality of life [23]. Only one clinical study did not observe any significant change after the application of ESWT [27]. The cost of one cycle of ESWT averages about $3,338 in the treatment of erectile dysfunction [28]. Given the similar number of applications, similar duration of therapy, and number of shock waves used as a baseline in most studies, comparable costs of treatment are assumed in PB as well.

Table 1. Extracorporeal shock therapy.

AUTHOR	TYPE OF RESEARCH	NUMBER OF PATIENTS	SHOCK IMPULSES PER SESSION	NUMBER OF SESSIONS	ENERGY	FINAL RESULT	SIDE ACTIONS
STREBEL 2004	Prospective	52	3000	5 * weekly interval	0.17 mJ/mm2	Reduction of penile pain	Minimal skin irritation
DE BERARDINIS 2010	-	157	2000	3,5	-	Reduction of pain and deviation	there are no signifi-cant ones
CHITALE 2010	Randomized, prospective, double-blind	36	3000	6 * weekly interval	38 MPa	Unchanged	there are no signifi-cant ones
SRIRANGAM 2006	Prospective	38	3000	3,4	0.11–0.17 mJ/mm2	Reduction of pain and deviation	there are no signifi-cant ones
PALMIERI 2009	Prospective, randomized, double-blind, placebo-controlled	100	2000	4 * weekly interval	0.25 mJ/mm2	Reduction of pain, improvement of erectile function and quality of life	there are no signifi-cant ones
HATZI-CHRISTODOUL OU 2013	Placebo-controlled, randomized, blinded, prospective	102	2000	6 * weekly interval	0.29 mJ/mm2	Reduction of pain	
DI MAURO 2019	Observational	325	3000	6 * weekly interval	0.25 mJ/mm2	Reduction of pain, deviation and plaque, improvement of erectile function, penis lengthening	there are no signifi-cant ones
ABDESSATER 2022	Prospective	39	4000	7,2	0.064 mJ mm-2 до 0.160 mJ mm-2	Reducing pain, deviation, plaque and improving erectile function	there are no signifi-cant ones
CHUNG 2015	Prospective, open	30	3000	12 *twice a week	0.25 mJ/ mm2	Reducing pain, deviation, plaque and improving erectile function	there are no signifi-cant ones

Therapeutical ultrasound

Ultrasound has been used to treat soft tissue injuries since the early 1930s [29]. The frequencies used to achieve a therapeutic effect are usually between 1.0 to 3.0 MHz. Low-frequency ultrasound waves have greater tissue penetration, but are less focused. Sound waves at a frequency of 1.0 MHz are absorbed at a depth of 3-5 cm and are recommended for deeper injuries and in patients with significant amounts of subcutaneous fat [30]. The ultrasound dose can be varied by changing the amplitude and intensity of the wave, and can be used in pulse or continuous mode [29]. The last form has a greater heating effect, as the approximate temperature reached is 40-45 degrees, which is necessary for optimal tissue treatment [29]. Thermal effects include increased blood flow, decreased muscle tone, increased extensibility of collagen fibers, decreased pain, and a pro-inflammatory response [29]. In a current, randomized, controlled trial of forty-six men with PD, the effectiveness of ultrasound therapy was evaluated. During 4 weeks, 12 ultrasound sessions were performed with a wave intensity of 1.5-2.5 W/cm2, a frequency of 3 MHz and a treatment duration of 10 minutes per session. The results show a significant reduction in the deviation of 17□ and an improvement in erectile function [31].

Intralesional therapies in the treatment of PB (Table 2)

Intralesional injections with verapamil and in combination. Verapamil is a calcium channel blocker that promotes wound healing [32]. A putative mechanism of action is thought to be reduced proline incorporation into the extracellular matrix of the tunica scar, thereby promoting collagen degradation [33,34].

The efficacy and safety of this therapy as part of treatment in Peyronie's disease has been the subject of a number of studies [35–44] (table 2). In most clinical studies, reduction of penile pain [37,38,43], stabilization of penile deformity [40,43], reduction of PD [35,36,38,40,41], improvement of EF [35,37] were observed. ,38,40,41], reduction of penile plaque [35,37,38,40–42], improvement of penile blood circulation [35,41], reduction of distal penile rigidity [40]. Only two of the studies showed no change after subsequent therapy [39,44]. The average annual cost of verapamil is about US$60 according to 2019 US data [45].

Intralesional injections with Interferon alpha 2B and in combination. Interferons are cytokines that have a wide range of medical applications. Specifically for PD, in vivo studies of fibroblasts involved in plaque formation in PD treated with Interferon alpha 2B resulted in a concentration-dependent inhibition of collagen production and fibroblast proliferation through upregulation of collagenase [46].

In one examination, a change in hemodynamic penile parameters was observed [47], (table 2). Other studies have shown a reduction in PD [48–50], a reduction in plaque and density, and also a reduction in pain [48], (see Table 2). Only one study did not observe any significant clinical changes [51], (see Table 2). The average cost of therapy is about $3,000. per year [45].

Intralesional injections of Clostridium histolyticum collagenase. In the early 1980s, Gelbard and colleagues found that purified clostridial collagenase was effective in degrading penile plaques under both in vitro and in vivo conditions [52,53]. Commercially purified collagenase Clostridium histolyticum (CCH), consisting of two microbial collagenases in a specific mass ratio, was applied. Collagenase AUX-I and collagenase AUX-II were isolated and purified from the fermentation of Clostridium histolyticum bacteria and are responsible for the degradation of collagen types I and III, which in turn are one of the main contributors to penile plaque formation [54]. Later, the same author published the clinical studies IMPRESS I and II, which are among the studies with the largest number of participating patients with PD [55], (table 2). These were 2 phase 3 randomized, placebo-controlled, double-blind studies, including 417 and 415 patients, respectively. Patients were in a stable phase of the disease and underwent 4 cycles of treatment separated by an interval of 6 weeks. Each cycle included 2 injections (24-72 hours apart) of CCH (0.25 mL, 0.58 mg) by single needle administration, followed by manual penile modeling 24-72 hours after the second injection. Patients with ventral deviation and extensive penile plaque calcification were excluded from the clinical trial. PD improvement was significantly greater in the CCH cohort compared to placebo (mean improvement 17° (34%) vs 9.3° (18.2%) respectively). The Peyronie disease symptom bother score questionnaire was also significantly better after CCH therapy. Side effects include bruising and hematoma, which are common, but 3 cases of corpora cavernosa rupture requiring surgical intervention have also been reported [55]. Based on these studies, the therapy has been officially

approved by the Federal Drug Administration (FDA) for use in the United States. In Europe, this therapy is not approved, and on December 5, 2019, the European Commission withdrew the marketing authorization for Xiapex (CCH) in the European Union (EU), but it is recommended as a therapy by the European Urological Association (EAU) [14].
Since then, more than 100 studies have been published showing intralesional CCH therapy with improvement in penile deviation (and erectile function), also describing a significant reduction in plaque volume [56–59], (Table 2). The price on an annual basis is stated to be around $18,000. [45].

Table 2. Intralesional therapies

AUTHOR	TYPE OF RESEARCH	NUMBER OF PATIENTS	APPLIED MEDICAMENT	NUMBER OF SESSIONS	FINAL RESULT	SIDE ACTIONS
SHIRAZI 2009	Randomized	80	Verapamil	-	Без промяна	there are no significant ones
BENNETT 2007	Prospective	48	Verapamil	6	Stabilization of penile deformity, reduction of pain	there are no significant ones
REHMAN 1998	Prospective	14	Verapamil	24	Reduction of plaque volume, improvement of erection	there are no significant ones
CAVALLINI 2007	Randomized, prospective	77	Verapamil	12	Improved deviation, reduced plaque, improved erectile function, improved penile blood circulation	hematoma
LEVINE 1997	Prospective	38	Verapamil	12	Reduction of plaque, penile deformity and distal rigidity, deviation, improvement of sexual function	there are no significant ones
GONTERO 2011	Randomized, prospective	29	Verapamil	12	No change in favor of verapamil	there are no significant ones
FAVILLA 2014	Randomized, prospective, controlled	105	Verapamil	12	Reducing plaque, pain, deviation and improving erectile function	there are no significant ones

DELL'ATTI 2015	Prospective, controlled	59	Verapamil	12	Reduction of plaque and pain, improvement of deviation and erectile function	there are no significant ones
ABERN 2012	Prospective	74	Verapamil	12	Deviation reduction	there are no significant ones
CAVALLINI 2002	Prospective	60	Verapamil		Improving erectile function, penile blood circulation, reducing plaque and deviation	there are no significant ones
INAL 2006	Randomized, prospective	30	Interferon 2alpha b	12	Unchanged	there are no significant ones
KENDIRCI 2005	Prospective, placebo controlled, parallel study	39	Interferon 2alpha b	6	Change in hemodynamic penile parameters	there are no significant ones
HELLSTROM 2006	Single blinded, multicenter, placebo controlled, in parallel	117	Interferon 2alpha b	24	Deviation reduction, plaque and density reduction, pain reduction	flu-like symptoms
TROST 2013	Retrospective	127	Interferon 2alpha b	6-24	Deviation reduction	there are no significant ones
STEWART 2015	Retrospective	131		6-24	Deviation reduction	there are no significant ones
GELBARD 2013 (IMPRESS I AND II)	Placebo-controlled, randomized, double-blind	832	Collagenase clostridium histolyticum	До 8	34% reduction in penile deviation, improvement of PDQ	rupture of the corpus cavernosum
AMIGHI 2020	Retrospective	152	CCH	Средно 8	Намаляване на пенилната девиация	reduction of side effects
FERNÁNDEZ-PASCUAL 2019	Pospective registry	144	CCH	-	Reduction of penile deviation	ecchymosis, bruising and pain in the penis
ANAISSIE 2017	Retrospective	77	CCH	8	Reduction of penile deviation	-
MELGAREJO-SEGURA 2021	Pospective, not randomized	13	CCH	6	19% reduction in penile deviation, improvement of IIEF and PDQ-Score, increase in length, girth of the penis	mild, confined to the penis
GENNARO 2015	Prospective, controlled	164	Hyaluronic acid	30	Plaque reduction,	there are no significant ones

					deflection improvement, stiffness enhancement	
ZUCCHI 2016	Prospective, controlled	65	Hyaluronic acid	10	Plaque reduction, deviation improvement, erectile function improvement and pain reduction	
FAVILLA 2017	Multicentered, prospective, randomized, double-blind	140	Hyaluronic acid	12	Reduction of plaque, deviation and improvement of erectile function	there are no significant ones
COCCI 2021	Opened, prospective	244	Hyaluronic acid	8	Plaque reduction, deviation improvement	there are no significant ones
CAI 2021	Prospective, randomized, phase 3	83	Hyaluronic acid	6	Improved deviation, improved erectile function	there are no significant ones

Hyaluronic acid. Hyaluronic acid is characterized by anti-inflammatory and immunosuppressive action. [60–62] Greater improvements in penile deviation and patient satisfaction have been reported compared with verapamil [63,64] (Table 2). The combination of intralesional administration and oral administration showed greater efficacy in reducing penile deviation and improving sexual function. [65]

Topical therapy for PB

Iontophoresis (EMDA, electromotive drug administration). Iontophoresis is a method using galvanic current to improve the penetration of drugs to the desired tissues - in this case the corpora cavernosa of the penis [66]. This therapy is administered as intravesical chemotherapy in muscle-invasive urothelial carcinoma of the bladder [66,67], interstitial and radiogenic cystitis, or in overactive bladder [67]. There are also several studies on PB. A 2003 study found that 71.5% of tunica albuginea samples from PD patients contained measurable levels of verapamil after topical application with EMDA [68]. The same scientific center conducted a randomized placebo-controlled trial with a small number of 23 patients, which showed a reduction in penile deviation without reaching a statistically significant result [69]. In contrast, another scientific group showed with a larger number of patients that verapamil and dexamethasone iontophoresis improved penile deviation to a greater extent than a lidocaine-treated control group [70]. EMDA of verapamil and dexamethasone may also reduce penile pain more effectively compared to intralesional injection of verapamil and dexamethasone [71].

H-100. H-100 is a topical agent intended for treatment during the acute phase of PD. It consists of emu oil, a transdermal carrier rich in fatty acids, as well as nicardipine and superoxide dismutase. It has been suggested that emu oil improves tissue penetration and could theoretically lead to an increase in the concentration of topical agents [72]. The H-100 pilot study involved randomizing 22 patients to treatment with H-100 or placebo for 3 months, followed by a 3-month crossover phase [73]. All patients in the clinical trial were in the acute phase of PD (duration <12 months). After 6 months of therapy, the group of patients treated with H-100 had a significant improvement in the length of the stretched penis (22.6%), a reduction in PD (40.8%), and a reduction in the average level of penile pain (85.7%) [73]. Although interesting, these findings require further clinical studies with a

larger number of patients to establish H-100 therapy as a first-line treatment modality in the acute phase of PD.

Penile Traction Therapy (PTT). PTT induced changes at the cellular level by applying mechanical force to the penis. Chung and colleagues used a cell culture system of PB cells to model the effect of PTT on tunica albuginea [74]. The study showed a significant increase in smooth muscle α-actin, β-catenin and Hsp 47 proteins in the PTT group compared to the control group. The analysis also showed an increase in the expression of metalloproteinase-8 (MMP) [74]. Collagen turnover and normal wound healing are regulated by various MMPs that influence cell survival, gene expression and ongoing activation of myofibroblasts [75,76]. In PD, MMPs are excessively inhibited, leading to excess collagen deposition in the extracellular matrix (ECM), which subsequently leads to plaque formation [77].

One of the first published studies of PTT in PB was a retrospective study of 10 men who underwent traction therapy for an average of 4.5 hours per day for 6 months. A 33% improvement in penile deviation (10°–45°), an increase in penile length of 0.5–2.0 cm and girth of 0.5–1.0 cm was observed and measured [78].

In a prospective study comparing 55 patients in the acute phase of PD who underwent PTT for 6 months with 41 patients who did not have such therapy, it resulted in a 20° improvement in PD and EF, a decrease of penile pain. Furthermore, penile plaques were not identified by ultrasound in 48% of patients after PTT [79]. In a multicenter, controlled study in patients with stable phase of PD who were randomly assigned to PTT with Penimaster PRO (MSP Concept, Berlin, Germany) for 12 weeks, a significant reduction in mean penile deviation of 31.2 was observed ° (41% improvement over baseline) and an increase in penile length of 1.8 cm. Patients in the PTT group were instructed to use the device for 3-8 hours per day. Men undergoing PTT for more than 6 hours per day had a significantly greater improvement in PD compared to those who used the device for less than 4 hours (51.4% vs. 28.8%). Mild side effects occurred in 43% of patients and included glans numbness and penile discomfort [80]. RestoreX is another new traction therapy device for Peyronie's disease. In a randomized, controlled, single-blind trial, patients with PD (n=110) with a mean preintervention PD of 59.3° were randomized to 30-90 minutes per day of PTT or no therapy in a 3:1 ratio. After 3 months, a significant improvement over placebo was observed in penile deviation (−11.7° vs. +1.3°) and increase in penile length (1.5 vs. 0 cm) [81]. The price of PTT for a ten-year basis is indicated at about 833 USD. with a RestoreX device [82].

Device for vacuum erection (penis pump, PP). PPs were originally introduced as a treatment for erectile dysfunction (ED). The use of PP in the treatment of PB is less studied. In a study investigating the molecular mechanisms of PP using a rat model, an increased smooth muscle/collagen ratio, preserved expression of smooth muscle α-actin and endothelial NO synthase (eNOS), while down-regulation of hypoxia factor- 1α (HIF-1α) and the apoptotic index, reduced expression of transforming growth factor beta (TGF-β) [83]. A further study using a rat model of PP showed a reduction in TGF-β1, preservation of smooth muscle α-actin, as well as a significant improvement in penile deviation and intracavernous pressure after PP therapy [84]. In patients with an average penile deviation of 48° who underwent 12 weeks of PP therapy, twice daily for 10 minutes per session, an improvement in penile deviation of 5°-25° was observed in 68% of men, while 10% have PD progression. 49% of patients required subsequent surgical correction [85]. In a recent clinical study examining the effect of extracorporeal shock wave treatment, no additional significant results were observed from an applied combination with PP [86].

Oral therapies for PB. Oral medications used in the treatment of PD fall into two general categories: antifibrotic and antioxidant medications. These drugs are attractive to many patients because of their non-invasive nature, affordability and supposed lack of side effects. Also for patients who may not be psychologically ready for intralesional injections or surgery [87].

Phosphodiesterase Type 5 Inhibitors (PDE5Is). PDE5Is are approved for the treatment of ED in Europe [14] and the USA [12] and remain the first-line treatment for ED in the absence of medical contraindications. Concomitant ED is present in 30–45% of patients with PD [7,88]. A 2002 study found that >70% of PD patients with concomitant ED who used sildenafil reported satisfactory erectile function without worsening of penile deformity or pain [89]. In addition to beneficial effects on erectile function, it is becoming increasingly clear that PDE5Is possess intrinsic antifibrotic properties that may help modulate fibrosis occurring in the tunica albuginea in PD [90]. Endothelial

nitric oxide synthase (NO) has antifibrotic properties. PDE5Is prevent the degradation of cyclic guanosine monophosphate (cGMP) to GMP, thereby maintaining an elevated level of circulating NO [91]. In a study, daily administration of sildenafil was shown to decrease the collagen/fibroblast ratio and induce fibroblast apoptosis in Peyronie's fibrotic plaque in a rat model [92]. When human PB plaques were exposed to sildenafil and pentoxifylline (a non-specific PDE5I inhibitor), the authors also found a reduction in smooth muscle collagen and alpha-actin [92]. Another study found that long-term administration of the substance vardenafil reduced collagen and the number of myofibroblasts in a Peyronie's fibrotic plaque in a rat model [93]. In a clinical study in 65 men with penile plaque in the penile septum, in 35 of the patients who were treated daily with the drug tadalafil (2.5 mg), the therapy resulted in an improvement in EF. In addition, penile plaque was reduced in 24/35 patients (69%) who were treated with tadalafil compared to 3/30 (10%) in the control group [94]. In another clinical trial comparing the combination of sildenafil + CCH (Clostridia histolyticum collagenase) and CCH alone in the treatment of PD, it was observed that the combination therapy was superior in terms of improving PD and EF [95]. Combination therapy with ESWT plus tadalafil 5 mg once daily also represents a valid conservative strategy in the treatment of patients with PB and ED [23].

Pentoxifylline. Pentoxifylline is a non-specific PDE inhibitor that has been studied in a variety of conditions, including PD [96]. Several retrospective series from single centers have been published. One study found that more than 91.9% of patients with calcified plaques from PB who were treated with pentoxifylline had their calcification levels stabilized or even improved compared to 44.4% of those who were not. were taking pentoxifylline. In those treated with pentoxifylline, the probability of subjective worsening of the clinical condition was much lower (25.0% vs. 78.3%) [97]. Another study observed that 26.7% and 73.3% of patients treated with oral pentoxifylline had a reduction in PD and penile pain, respectively. These results are similar to those of patients undergoing intralesional verapamil [98]. In another study, intralesional administration of pentoxifylline, in combination with antioxidants and topical diclofenac, reduced penile deviation by 10° in men with acute PD [99].

L-arginine and L-citrulline. L-arginine is an amino acid and precursor of nitric oxide (NO), a potent vasodilator that acts at the level of cavernous smooth muscle cells to induce erection [100]. NO also has important antioxidant properties that make it a suitable candidate for PD therapies [101]. L-arginine is a promising substance in combination with intralesional therapy with verapamil +/- PTT, although the direct effect of L-arginine is unclear [36]. Oral L-arginine has several drawbacks. For example, arginine undergoes extensive first-pass metabolism in the liver (approximately 38%), resulting in a lower available circulating concentration [102]. Additionally, side effects, including gastrointestinal disorders and diarrhea, limit use in some patients [103]. Upon oral administration, citrulline is converted to arginine in vivo [104]. L-arginine and L-citrulline can be considered as non-invasive treatment options, especially in the setting of combination therapy with other non-invasive options during the active phase of PD [36]

Vitamin E. Vitamin E consists of eight fat-soluble compounds, the so-called tocopherols and tocotrienols, which are usually obtained from vegetable oils. Vitamin E has antiproliferative and antioxidant properties [105]. The proposed mechanism of action involves a reduction in collagen deposition due to free radical scavenging [106]. In a randomized trial, patients receiving vitamin E and propionyl-L-carnitine alone, in combination, or placebo for 6 months showed no significant difference in penile pain or reduction in PD and plaque [107]. Another study reported similar improvements in objective outcomes and subjective complaints in men in the acute phase of PD who were treated with intralesional Interferon alpha 2B, vitamin E, or a combination [51]. In contrast, Paulis and colleagues reported a significant reduction in PD after treatment with a combination of verapamil, blueberries, propolis, topical diclofenac, and vitamin E (12.25°) versus topical diclofenac without vitamin E (6.73°) [108].

Selective Estrogen Receptor Modulator (SERM). Tamoxifen, a selective estrogen receptor modulator (SER), downregulates transforming growth factor (TGF-β)-mediated signaling in myofibroblasts, which is considered an important component of the putative pathophysiology in the development of PD [3,4,109]. Very few studies have been conducted with tamoxifen in its context of therapy in patients with PD. One of the first published studies found that penile pain was reduced in 80% and penile deformity in 35% of patients treated with tamoxifen [110]. Another small randomized trial of 25 patients compared tamoxifen versus placebo for 3 months. The results showed that there

was no significant difference in the improvement of penile pain and penile deviation or reduction of penile plaque between the two groups [111]. Another study found that oral L-citrulline more effectively reduced penile pain and prevented disease progression compared to tamoxifen [112]. However, combination therapy with tamoxifen and PDE5I may have a synergistic antifibrotic effect, thereby reducing the occurrence of myofibroblastic transformation and extracellular matrix production [113].

Colchicine. Colchicine has been used to treat gout by preventing the mobilization of inflammatory mediators by inhibiting microtubules [114]. In scientific work with a rat model of PB, colchicine was also found to inhibit collagen deposition [115,116]. One of the earliest studies evaluating colchicine in BP was a pilot study in 24 patients. The authors found that PD improved in 7/19 (37%) and penile pain relief was reported in 7/9 patients (78%) [117]. In a subsequent study, PD was observed to improve in 30% and worsen in 22% of patients treated with colchicine in the acute phase of PD. Shorter disease duration, less pronounced PD (<30°) and absence of vascular risk factors are associated with better outcomes [118]. In a small randomized trial, a group of 45 patients with acute PD (disease duration <6 months) and relatively mild PD (<30°) compared ibuprofen versus colchicine in combination with vitamin E for 6 months. The authors found that a significantly greater percentage of patients in the colchicine/vitamin E group reported improvement in PD (48% vs. 18%) [119]. Another randomized controlled trial comparing colchicine with placebo found no significant differences in objective outcomes between the treatment and control arms in penile deviation, reduction of penile plaque, or pain [120]. It is important to note that the most common side effects reported with colchicine use include gastrointestinal disorders and diarrhea, but more severe conditions have also been observed, including myelosuppression and even neuromuscular toxicity [114].

Potassium paraaminobenzoate (Potaba). Potaba inhibits fibroblast activity through increased monoamine oxidase activity, reduces acid mucopolysaccharide and glycosaminoglycan secretion, and has anti-inflammatory properties [121]. Although older published placebo-controlled, randomized trials with Potaba reported mixed clinical results, in terms of delaying disease progression and reducing penile pain, its positive impact on PD was limited [122,123]. A recent study found that 68 % of patients treated with potaba discontinued therapy, citing side effects, lack of efficacy, and cost as determining factors [124]. Side effects include gastrointestinal disorders, pruritus, fever, rash, and in rare cases even liver dysfunction [122,124,125]. In addition, potaba is taken 4 times a day, which makes regular intake difficult. Given the lack of reliable data to support clinically meaningful benefits, the significant side effect profile, and the dosing schedule, potaba is rarely used for the treatment of BP in the modern era and is not recommended by the European (EUA) [14] and American (AUA)) [12] urological associations.

Radiotherapy. Low-dose surface radiotherapy is used to treat PB. An increase in NO synthase along with anti-inflammatory effects has been suggested as a mechanism of action [126]. However, radiotherapy carries the risk of penile fibrosis as well as damage to peripheral arteries and nerves leading to ED [127]. Evidence for the use of radiotherapy in PB is primarily based on case series with non-standardized protocols. One scientific review suggested that radiotherapy may improve painful erections but without improvement in penile deviation [128]. Further reviews of the literature by Tsambarlis [13] and Mulhall [128] concluded that the potential penile damage associated with radiotherapy outweighed any potential beneficial effect.

Regenerative therapy: stem cells and platelet-rich plasma. Although stem cells are not technically a drug, their application is similar, such as intralesional injection therapy. In recent years, cellular technology based on stem cell therapy (SCT) has been used to treat PD [129,130]. Although the exact mechanism of action of SKT in PD remains largely unknown, it is believed that intralesional injection of stem cells would have an immunomodulatory effect through its anti-inflammatory and antifibrotic actions, as well as decrease the expression of tissue inhibitors of metalloproteinases and increase the expression of matrix metalloproteinases thus reducing plaque in PD [5]. Furthermore, it has been shown that intralesional allogeneic adipose stem cells can decrease the expression of tissue inhibitors of metalloproteinases and increase the expression of matrix metalloproteinases [131] while inhibiting the Rho/RhoA and SMAD signaling pathways responsible for myofibroblastic activity [132]. Although several basic science studies of intralesional SCT in animal models of PD have shown encouraging results [133–136], its translation into clinical trials has been difficult and very limited with suboptimal clinical outcomes. The effects of different types of SCT on penile plaque remodeling and longer-term clinical efficacy, durability, and safety need further studies. To date, one known

human study of SCT in PD has been published using penile injection of placental matrix-derived mesenchymal stem cells (PMD-MSC), after which 7 out of 10 PMD-MSC-injected plaques disappeared completely at the 3-month review. No significant improvements in penile size or penile blood supply were observed [137]. Other currently ongoing registered clinical trials of SCT include cultured allogeneic adult umbilical cord stem cells [NCT05147779] and autologous stromal vascular fraction [NCT04771442].

In recent years, there has been considerable interest in the role of platelet-rich plasma (PRP) as an alternative to SCT due to its easier preparation and justified safety profile [138].

Although several animal studies of PRP in PD have been conducted [139], only one randomized, double-blind, placebo-controlled, crossover human trial on the efficacy and safety of platelet-rich plasma has been reported to date with an expected completion date of the study in mid-2023 [NCT04512287].

Botulinum Toxin (Botox). There is considerable interest in expanding the use of botulinum toxin to treat conditions in the field of sexual medicine, although the exact mechanism of action in PB remains largely unknown [140]. The role of intralesional Botox injection was investigated in a randomized, placebo-controlled, crossover, single-center trial. In this pilot study with 6 patients, a 21.7% improvement in penile deviation was found in patients who received 100 units of Botox injection [NCT00812838].

Discussion: PB is a connective tissue disease and is often characterized by the presence of an (inflammatory) plaque in the bilaminar tunica albuginea, secondary to aberrant wound healing and abnormal genetic neurohumoral pathways [3,14]. Also, frequent penile microtraumas are considered the most common onset of the disease [1]. Current in vivo models of PB emphasize that TGF-β1-mediated activation of myofibroblasts appears to be the common denominator of PB [3,4] and therefore drugs aimed at inhibiting the TGF-β1 pathway and myofibroblastic transformation are of interest and likely form a new frontier in PD therapy [3,5]. Drugs that enhance the expression of tissue inhibitors of metalloproteinases and/or suppress the function of matrix metalloproteinases would provide a new way to restore the balance between profibrotic and antifibrotic responses at the cellular level. Studies in next-generation genetic sequencing and transcriptional biomarker regulatory pathways in PD will provide useful insights into the pathophysiology of PD and support the development of future regenerative technologies, including cell-based therapies targeting various antifibrotic molecular mechanisms with the potential to integrate into the existing arsenal for the treatment of PB [5].

It is important to note that no universal therapy for PB has been discovered so far.

There are various non-invasive therapies for PB, as surgical treatment is contraindicated in the acute phase of PB. Current clinical guidelines for the treatment of PB recommend the use of oral medications as first-line treatment, although scientific evidence is relatively scarce and published studies are characterized by significant heterogeneity of methodologies, such as small patient numbers, mixed characteristics of PB and limited objective performance indicators. One of the reasons for the reduced efficacy of oral therapy is related to the lack of local absorption and penetration of the drug to achieve a sufficient concentration of the drug in the penile plaque. Oral medications may be helpful in the early phase of PB with unstable or progressive penile curvature, when the inflammatory plaque is not yet fully formed. Also, in men who do not want surgery, oral medications can be used as an adjunct to other nonsurgical therapy. Randomized placebo-controlled trials are needed to evaluate the treatment efficacy and use of PDE5Is in patients with PD. In the meantime, in the absence of clear medical contraindications, the use of PDE5Is should be considered as a useful adjunct for patients with PD, especially for reduced erectile function [12,14] and penile pain. In a clinical study, it was shown that therapy with tadalafil led to the reduction of penile plaque [94]. Transdermal administration of drugs with or without iontophoresis is used in patients with penile pain.

Inhomogeneous data are found on the financial toxicity of the mentioned therapies, and the most important for an objective comparison are the ten-year costs, for which there is limited information. Comparison of different therapies from a financial point of view is also hampered by dynamically rising costs [82]. There is also a significant price difference between the US and Europe. For example, an intralesional application in a US article is listed as US$300[45]. Although intralesionally administered drugs are theoretically expected to be more effective than oral drugs due to the targeted direct effect in the penile plaque, published clinical studies show mixed results and this

reflects the heterogeneous nature of PD with different manifestations. Examples include atypical disease, sometimes the absence of a palpable plaque for injection, the level of clinical experience in performing intralesional therapy, and optimal intralesional treatment protocols [5,141]. Placebo-controlled studies have shown that saline injection and injection volume can improve penile deviation and plaque size [12,14,142]. Data suggest, for example, that in the intralesional application of CCH, the injection technique is important [58]. Studies are available that speak to the importance of the combination of different approaches [58]. The combination of sildenafil + CCH versus CCH alone showed that combination therapy was superior in improving penile deviation and erectile dysfunction [95]. Furthermore, penile remodeling was not commonly applied during intralesional therapy prior to the publication of the IMPRESS study [55], and the lack of manual remodeling may play a role in the suboptimal results observed with therapy with other intralesional drugs [5]. To date, CCH remains the only licensed drug in PD. However, CCH is a very expensive, possibly cost-effective therapy compared to definitive penile reconstructive surgery, and of limited availability in Europe.

The possibilities for a direct comparison of the results of shock wave therapy are limited in view of the differences in the equipment used, the different protocols (number of sessions, energy, type, number of waves, time distribution of the procedures) and the different therapists. The data on the costs of the described therapies place them in a relatively high price range, which on the one hand is explained by the specific substances, respectively specialized equipment for their implementation and the duration of each individual procedure [28].

Given its non-invasive nature and lack of significant side effects, PTT [80,81] can be considered first-line therapy for men with BP, especially in those concerned about possible loss of penile length. However, PTT traditionally requires very high motivation from the patient, who is committed to hours of daily therapy. New data with the RestoreX device show that shorter-term therapy may still offer clinically meaningful results.

Conclusion.

A multidisciplinary approach including various oral and/or intralesional pharmacotherapies, therapeutic ultrasound, extracorporeal shock wave therapy, along with mechanical devices in combination with clinical psychosexual therapy when necessary, could provide a more effective treatment of PD to prevent or at least to delay the need for definitive penile reconstructive surgery.
Larger, multicenter clinical trials with uniform study methodology and treatment protocols with greater emphasis on patient-reported outcomes, with analysis of the cost-effectiveness of a given therapy, are needed. Using generated proteomic, genomic and metabolomic data will be useful for future treatment of PD.

Greater public awareness and patient education on issues related to the treatment of PD are needed to streamline the clinical pathway in the treatment of this heterogeneous and yet complex psychosexual condition

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