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Minimally invasive treatment of Peyronie's disease: evidence-based progress

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Peyronie's disease (PD) is often physically and psychologically devastating for patients, and the goal of treatment is to improve symptoms and sexual function without adding treatment-related morbidity. The potential for treatment-related morbidity after more invasive interventions, e.g. surgery, creates a need for effective minimally invasive treatments. We critically examined the available literature using levels of evidence to determine the reported support for each treatment. Most available minimally invasive treatments lack critical support for effectiveness due to the absence of randomised, placebo-controlled trials (RCTs) or non-significant results after RCTs. Iontophoresis, oral therapies (vitamin E, potassium para-aminobenzoate, tamoxifen, carnitine, and colchicine), extracorporeal shockwave therapy, and intralesional injection with verapamil or nicardipine have shown mixed or negative results. Treatments that have decreased penile curvature deformity in Level 1 or Level 2 evidence-based, placebo-controlled studies include intralesional injection with interferon α-2b or collagenase clostridium histolyticum.

Keywords

penile induration, randomised controlled trials as topic, placebos

Key Messages

PD is now understood to be a chronic disease with the need for symptom management from disease onset throughout the lifetime of the patient.

Effective minimally invasive treatment options are highly desired by patients.

The minimally invasive treatments with the highest level of evidence supporting effectiveness in improvement of penile curvature deformity include intralesional injections using interferon α-2b or collagenase clostridium histolyticum.

Recognition of PD and initiation of an evidence-based minimally invasive treatment are key to improving patient outcomes.

Introduction

The management of Peyronie's disease (PD) remains a challenge. The prevalence of PD is estimated at up to 7% among men in the general population, up to 8% of men with erectile dysfunction (ED), and >20% of men with comorbid diabetes and ED [1–3]. Importantly, these prevalence estimates may yet underestimate the true incidence of PD, because men may not present for treatment due to embarrassment or the misconception that the disorder is not treatable. Additionally, men who lack erections or who are not sexually active may not present for treatment due to lack of awareness of PD. Effective treatment is important, as PD can be physically and psychologically devastating for patients and may negatively impact partner relationships [4,5]. Through the course of PD, one or more collagen plaques develop in the tunica albuginea, and penile inflammation, fibrosis, induration, and possibly penile pain typically occur. Penile deformity that occurs during erection, such as penile curvature, shortening, hourglass narrowing, or a hinge effect, may prevent intercourse or result in greater awkwardness, performance anxiety, and less sexual enjoyment. Although the aetiology and underlying pathophysiology of PD are not yet well understood, genetic predisposition, trauma, and inflammation are thought to play a critical role [6,7].

PD is often a progressive disorder, and the usual course has two phases distinguishable by symptom presentation. During the early or acute disease phase, the palpable collagen plaque is still forming with associated inflammation. Patients may experience painful erections and curvature deformity of the erect penis. Not all patients with PD experience penile pain or discomfort, and if present, it typically resolves by 12–18 months after disease onset [8]. Calcification of the plaque may occur at any time during the disease course.

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The transition to the chronic phase of disease is marked by the resolution of pain and inflammation, and the plaque size and curvature become relatively stable with extensive fibrosis. Studies describing the natural course of PD have clearly shown that PD does not resolve on its own for most patients after the acute phase ends [8–10]. Rather than disease remission in the absence of treatment, 30–48% of patients have reported worsening disease from disease onset through the first year, and 40–67% have reported stable disease [8–10]. PD is now understood to be a chronic disease with the need for symptom management from disease onset throughout the lifetime of the patient. The current review provides an overview of the available minimally invasive treatment options for patients with PD and critically reviews available treatments using a rigorous level-of-evidence approach.

Materials and Methods

Relevant articles for the present review of evidence-based treatment studies were identified through MEDLINE and EMBASE databases. MEDLINE Medical Subject Headings (MeSH) terms included 'penile induration', 'randomized controlled trials as topic', and 'placebos'. The MeSH term 'penile induration' included the following entry terms in the search: 'penile fibromatosis', 'Peyronie's disease', 'plastic induration of the penis', 'fibrous cavernitis', and 'fibrous cavernitides'. The MEDLINE and EMBASE searches used the following terms: ('Peyronie' OR 'penile fibromatosis' OR 'penile induration') AND ('randomized controlled trial' OR 'randomized clinical trial' OR 'RCT' OR 'placebo') AND (*name of treatment*). Both the MEDLINE and EMBASE searches included the following treatment terms: 'topical verapamil', 'topical corticosteroids', 'vitamin E', 'tamoxifen', 'carnitine/propionyl-L-carnitine/acetyl-L carnitine', 'colchicine', 'potassium para-aminobenzoate/Potaba', 'pentoxifylline', 'phosphodiesterase-5 (PDE5) inhibitors', 'electromotive drug administration (EMDA)/iontophoresis', 'extracorporeal shockwave therapy (ESWT)', 'penile traction/penile mechanical stretching', 'intralesional injection', 'intralesional injection verapamil', 'intralesional injection interferon (IFN) α-2b', and 'intralesional injection collagenase clostridium histolyticum (CCH)'. Due to the limited availability of randomised, placebo-controlled trials (RCTs) in patients with PD, no year limits were used in the searches. Studies that met the inclusion criteria were published between 1997 and 2013.

The strategy to critically evaluate minimally invasive PD treatment studies was based on the Oxford Centre for Evidence-Based Medicine criteria. Level 1 studies were defined as high-quality RCTs with the characteristics of ≥50 patients enrolled, single- or double-blind design, patient outcome follow-up of ≥3 months, and use of objective and standard accepted outcome measures for penile curvature deformity (e.g. intracavernosal injection with angle determination using a goniometer protractor). Level 2 studies were defined as lesser quality RCTs. Level 2 studies used intracavernosal injection with angle determination using a goniometer protractor or photography to determine penile curvature deformity; however, these studies did not meet one or more of the remaining criteria for a Level 1 study (Table 1). Nonrandomised and non-placebo-controlled studies were excluded from this review.

Table 1 Levels of evidence criteria defining Level 1 and Level 2 RCTs.

Level 1	Level 2
Randomised, placebo-controlled	Randomised, placebo-controlled
≥50 patients enrolled	One or more criteria involving sample size, blinded design, or patient outcome follow-up duration do not meet Level 1 standard
Single- or double-blind design	
Patient outcome follow-up ≥3 months	
Objective, standard accepted outcome measure for penile curvature deformity using intracavernosal injection with goniometer protractor angle determination	Objective measure for penile curvature deformity using intracavernosal injection with goniometer protractor angle determination or photography

Results

Minimally Invasive Treatments

Minimally invasive treatments are aimed at shortening the acute phase of PD, stabilising the penile plaque, decreasing disease progression, or decreasing penile curvature. Such treatments are appropriate for men with unstable or progressive penile deformity, painful erections, or those with obscure plaques but are not interested in surgery [11]. Various minimally invasive treatments have been used in patients with PD, encompassing topical agents, oral systemic agents, mechanical stretching, ESWT, EMDA/iontophoresis, and intralesional injection [11]. These treatments differ in their methods of application, proposed mechanisms of action, and potential for adverse events.

Topical Therapy

Verapamil, a calcium channel blocker, is a topical agent that remains in frequent use as a first-line therapy. The potential action of verapamil in the treatment of PD is suggested by *in vitro* studies showing increases in the activity of collagenase, reduced fibroblast proliferation, and inhibition of local extracellular matrix production by fibroblasts [12,13]. However, it has been shown that topical treatment with verapamil does not penetrate the tunica albuginea, and thus has no scientific basis for treatment effect in PD [11,14].

Oral Therapy

Oral agents could be considered non-invasive relative to surgery; although for the purposes of this review we have considered them to be minimally invasive, as these agents do have effects subsequent to entering the body. Oral, systemic

treatment agents include vitamin E, Potaba, tamoxifen, carnitine, colchicine, and phosphodiesterase (PDE) manipulators, such as pentoxifylline and PDE5 inhibitors. Vitamin E is hypothesised to have an antioxidant effect, reducing oxygen free radicals and resulting in reduced plaque size, penile curvature, and collagen deposition in PD. Vitamin E, taken once or twice daily, is a frequently used treatment in patients with PD, as it is inexpensive and has few reported side-effects. However, there is conflicting evidence as to long-term cardiovascular effects of vitamin E usage at large doses, which urologists use for PD treatment [15–17].

Potaba is thought to have anti-inflammatory and antifibrotic effects through its enhancement of antifibrotic tissue properties, including increased oxygen uptake, an inhibitory effect on fibroblast glycosaminoglycan secretion, and stabilisation of monoamine oxidase activity [18]. Potaba is not a frequently used treatment as it is expensive, requires multiple daily dosing (e.g. 4×/day), and produces gastrointestinal side-effects [18,19].

Tamoxifen is proposed to modulate the release of TGFβ from fibroblasts and potentially reduce fibrogenesis [20,21]. It is taken twice daily, and side-effects may include headaches, nausea, vomiting, and decreased libido.

Acetyl-L-carnitine and propionyl-L-carnitine are proposed to inhibit acetyl coenzyme-A and produce an antiproliferative effect on human endothelial cells, which may then effect inflammation and fibrosis associated with PD [19,22]. They are taken twice daily and are well tolerated by patients.

Colchicine is an antimicrotubule agent hypothesised to treat PD through inhibition of collagen secretion from fibroblasts and blocking wound contraction [19]. It is taken daily, and patients typically experience gastrointestinal adverse effects.

Pentoxifylline is a nonspecific PDE manipulator with anti-inflammatory and antifibrogenic effects demonstrated *in vitro* and in a rat model of PD [23]. Adverse effects include nausea, vomiting, and dyspepsia; blood pressure should be monitored during treatment because of the potential for hypotension due to peripheral vasodilation. PDE5 inhibitors increase cyclic guanosine monophosphate levels and act as antifibrotic agents, as shown in rat models of PD [23,24].

Traction Therapy

Mechanical stretching or traction therapy is proposed to work through stretching the plaque, which is mechanically remodelled over time, to minimise loss of penile length and improve penile curvature and indentation [25]. Treatment can be uncomfortable and inconvenient due to use of the device 2–8 h daily for an extended period, but has been shown to be tolerated by highly motivated patients [25].

ESWT

The molecular mechanism of action has not been defined in ESWT; however, shockwaves are used to disrupt the dense tissue of the scar or plaque [26]. Treatment occurs over weekly sessions and is well tolerated [26,27]. Adverse effects include superficial bruising over the treatment site that required no analgesia [26,27].

EMDA/Iontophoresis

EMDA/iontophoresis, with application of verapamil or combined verapamil and dexamethasone, is thought to enhance transcutaneous absorption of the drugs through direct electrophoresis, electro-osmosis, or enhanced diffusion using surface-delivered heat or current [28]. Treatment occurs two to four times weekly over 2–3 months and is well tolerated, with the common adverse effect of temporary mild erythema at the treatment site [28,29]. The proposed mechanism of enhanced absorption of drugs is supported by a study showing verapamil detection in 72% of tunica albuginea specimens after EMDA, although verapamil levels ranged widely [30]. This contrasts with the finding that topical treatment with verapamil does not penetrate the tunica albuginea [11,14].

Intralesional Injections

Current treatment with intralesional injections directly into the penile plaque includes verapamil, nicardipine, IFN α-2b, and CCH. Verapamil and nicardipine, both calcium channel antagonists, are injected from once every other week to once or twice weekly for several weeks to several months and are well tolerated with minor adverse effects (i.e. transient ecchymosis/bruise) related to the injection [13,31,32].

The potential effectiveness of intralesional IFN α-2b in treating PD was suggested by an *in vitro* study in which IFN α-2b decreased the rate of *in vitro* proliferation, dose dependently, of fibroblasts derived from Peyronie's plaques, reduced the production of extracellular collagen, and increased the production of collagenase [33]. The IFN α-2b treatment protocol has varied, including 5×10^6 U every other week for 12 weeks [34] and 2×10^6 U twice weekly for 6 weeks [35]. Mild to moderate adverse effects include myalgias, arthralgias, sinusitis, flu-like symptoms with fever and chills, and minor penile swelling with ecchymosis [34–36].

CCH is now approved by the Food and Drug Administration (FDA) for PD in adult men with a palpable plaque and a curvature deformity of ≥30° at the start of therapy. It is a purified mix of two collagenases, AUX-I and AUX-II, that act as a 'chemical incision' to dissolve collagen [37–40]. CCH is injected directly into the primary plaque at the point of maximal penile curvature. After the second injection of each treatment cycle, modelling, which involves gradual, gentle

stretching of the flaccid penis in the opposite direction of the penile curvature deformity, is used to further reduce the restrictive effects of the plaque on tunica albuginea expansion during erection. The treatment protocol consists of two injections of CCH 0.58 mg (10 000 U) given 24–72 h apart. This cycle has been repeated after 6 weeks for up to four treatment cycles. Adverse effects were typically transient and most commonly included injection site tenderness, oedema, pain, and bruising [37,39,40]. More rarely, the serious adverse event of corporal rupture requiring surgical repair can occur. Three such corporal ruptures were reported among the 551 CCH-treated patients [37–40]. The use of CCH has only been examined in studies using regimens with several independent treatments, which would require multiple patient visits in a clinical setting. Finally, further study is needed outside of clinical studies to determine the effects of real-world use of CCH.

Level of Evidence for Minimally Invasive Treatments

The available RCTs are examined below to determine the Level 1 or Level 2 study evidence base for minimally invasive PD treatments, using criteria guided by the Oxford Centre for Evidence-Based Medicine criteria (Table 2) [13,18,20,26–29,31,32,34–37,39–41].

Topical Therapy

One study was identified as a RCT examination of topical treatment with verapamil; however, the study did not reach a Level 1 or Level 2 evidence base due to the lack of objective measurement of penile curvature deformity [42].

Oral Therapy

No Level 1 or Level 2 studies have examined the use of vitamin E, carnitine, colchicine, the PDE manipulator pentoxifylline, or PDE5 inhibitors in the treatment of PD. In a Level 1 study of treatment with Potaba, response was defined as full resolution, reduction in plaque size, and/or reduction in penile curvature of at least 30%. The study found that treatment with Potaba was associated with greater rates of study-defined response ($P = 0.016$), as well as decreased mean plaque size ($P = 0.04$) compared with placebo. Potaba and placebo did not differ significantly in reductions in pre-existing penile curvature deformity ($P = 0.07$) or pain, although a significantly higher rate of deterioration of curvature was seen in the placebo compared with the Potaba group ($P = 0.001$) [18]. A Level 2 study of tamoxifen did not result in improved penile curvature deformity, plaque size, or penile pain compared with placebo [20].

ESWT

No improvement in penile curvature deformity or plaque size has been shown in placebo-controlled trials using ESWT. In a Level 1 study, no significant change in mean plaque size or mean penile curvature deformity was found in the ESWT group compared with baseline [26]. Patients receiving ESWT did have statistically significant but not clinically meaningful lower mean penile curvature deformity and mean plaque size at 6 months compared with placebo due to the progressive worsening of disease in the placebo group [26]. In a Level 2 study, no differences in penile curvature deformity, plaque size, or penile pain were found following short-term ESWT compared with sham therapy [27].

EMDA/Iontophoresis

The Level 1 and Level 2 evidence base is mixed for EMDA/iontophoresis. EMDA with verapamil (Level 2 study) did not significantly decrease penile curvature deformity compared with placebo [28]. Notably, >50% of the patients who received placebo showed improvement in penile curvature deformity, suggesting possible healing or remodelling effects of the electrical energy alone [28]. In contrast, a study using lidocaine as the placebo control (Level 2 study) showed verapamil plus dexamethasone significantly decreased median plaque volume (824 to 348 mm^3) and penile curvature deformity (43° to 21°) compared with no change in patients receiving lidocaine [29]. Rather than being a true placebo condition, it was suggested that lidocaine may stabilise membranes and actually decrease the potential PD improvement that occurs as a result of the electrical energy itself, resulting in the treatment group differences at follow-up assessment [28]. In an early partial crossover study (Level 2 study) of EMDA with orgotein, dexamethasone, and lidocaine, a greater percentage of patients showed decreased penile curvature deformity, plaque size, and penile pain compared with placebo [41].

Penile Traction

Due to the limited, uncontrolled evaluation of traction therapy in PD, evidence-based treatment effects are not yet determined.

Intralesional Injections

Historically, injectable corticosteroids have been used for the treatment of PD. However, objective evidence of effectiveness is lacking and potential adverse effects include tissue atrophy and destruction of penile tissue planes [11,19]. Intralesional injections with verapamil, nicardipine, IFN α-2b, and CCH are each supported by Level 1 or Level 2 evidence-based studies [13,32,34–37,39,40]. A Level 2 study showed intralesional injection of verapamil significantly decreased plaque volume (from 1.42 to 0.63 mL) compared with saline placebo injection (which increased from 1.37 to 1.39 mL, $P < 0.04$) [13]. Penile curvature deformity improved from a mean (SEM) of 37.71° (9.3°) to 29.57°(7.3°) in 29% of verapamil patients vs no

Table 2 Level 1 and Level 2 evidence-based RCTs of minimally invasive treatments for PD.

Treatment study*	Design/N/duration, months Evidence level	Therapy + comparator	Treatment outcomes
Oral			
Potaba			
Weidner et al. (2005) [18]	Double-blind/103/12 Level 1	Potaba 3 g 4×/day for 12 months + Placebo	Increased response (full resolution, reduction in plaque size, and/or reduction in penile curvature of at least 30%)† Decreased mean plaque size† NS improved penile curvature and pain from baseline, but decreased deterioration of penile curvature vs placebo‡
Tamoxifen			
Teloken et al. (1999) [20]	Not blinded/25/4 Level 2	Tamoxifen 20 mg twice daily for 3 months + Placebo	NS between groups in improved penile curvature, plaque size, and pain
ESWT			
Palmieri et al. (2009) [26]	Double-blind/100/6 Level 1	ESWT 2000 focused shockwaves 1×/week for 4 weeks + Placebo (non-functioning transducer)	NS improved penile curvature and plaque size from baseline, but decreased worsening of penile curvature and plaque size vs placebo† Decreased pain‡
Chitale et al. (2010) [27]	Double-blind/36/6 Level 2	ESWT 1×/week for 6 weeks + Placebo (sham treatment)	NS between groups in improved penile curvature, plaque size, and pain
EMDA			
Greenfield et al. (2007) [28]	Double-blind/42/3 Level 2	EMDA 2.4 mA for 20 min with verapamil 10 mg in 4 mL saline 2×/week for 3 months + Placebo (4 mL saline)	NS between groups in improved penile curvature
Di Stasi et al. (2004) [29]	Double-blind/96/1.5 Level 2	EMDA 2.4 mA for 20 min with verapamil 5 mg and dexamethasone 8 mg 4×/week for 6 weeks + Placebo (2% lidocaine)	Decreased penile curvature‡ Decreased median plaque volume‡ NS between groups in pain
Montorsi et al.(2000) [41]	Double-blind/40/3 Level 2	EMDA 3 mA for 20 min with orgotein 8 mg, dexamethasone 8 mg, and lidocaine 120 mg 3×/week for 3 weeks + Placebo	Decreased penile curvature† Decreased plaque size† Decreased pain‡
Intralesional injection			
Verapamil			
Rehman et al. (1998) [13]	Single-blind/14/6 Level 2	Verapamil 10–27 mg, one injection/week for 6 months + Placebo (saline)	Trend toward decreased penile curvature¶ Decreased plaque volume† NS between groups in pain**
Shirazi et al. (2009) [31]	Single-blind/80/6 Level 1	Verapamil 10 mg, two injections/week for 3 months + Placebo (saline)	NS between groups in improved penile curvature, plaque size, and pain
Nicardipine			
Soh et al. (2010) [32]	Single-blind/74/12 Level 1	Nicardipine 10 mg, one injection every other week for 2.5 months, total of six injections + Placebo (saline)	NS between groups in improved penile curvature Decreased plaque size‡ Decreased pain†
IFN α-2b			
Hellstrom et al. (2006) [34]	Single-blind/117/3 Level 1	IFN α-2b 5×10^6 U, one injection every other week for 3 months + Placebo (saline)	Decreased penile curvature† Decreased plaque size‡ Decreased pain**
Dang et al. (2004) [35]	Not blinded/25/3 Level 2	IFN α-2b 2×10^6 U, two injections/week for 1.5 months + Placebo (saline)	Decreased penile curvature** Decreased pain**
Judge and Wisniewski (1997) [36]	Not blinded/13/1.5 Level 2	IFN α-2b 1.5 MU, three injections/week for 3 weeks + Placebo (saline)	Decreased penile curvature** Decreased pain**
CCH			
Gelbard et al. (1993) [37]	Double-blind/49/3 Level 2	CCH single injection (6000–14 000 U) + Placebo (saline)	More 'positive responders' (decreased penile curvature and plaque size)†

Table 2 Continued

Treatment study*	Design/N/duration, months Evidence level	Therapy + comparator	Treatment outcomes
Gelbard et al. (2012) [39]	Double-blind/147/9 Level 1	CCH 0.58 mg (10 000 U), two injections given 24–72 h apart and repeated after 6 weeks for up to three cycles + Placebo (saline)	Decreased penile curvature† Decreased plaque area**
Gelbard et al. (2013) [40]	Double-blind/832/12	CCH 0.58 mg (10 000 U), two injections given 24–72 h apart and repeated after 6 weeks for up to four cycles + Placebo (saline)	Decreased penile curvature§

**Currently no RCTs examining topical verapamil, oral treatment with vitamin E, carnitine, colchicine, the PDE manipulator pentoxifylline or PDE5 manipulators, or penile traction are available; †P < 0.05 treatment group vs placebo group; ‡P ≤ 0.001 treatment group vs placebo group; §P < 0.001 treatment group vs placebo group; ¶P < 0.07 treatment group vs placebo group. **No statistical comparisons provided. NS, nonsignificant; Potaba, potassium para-aminobenzoate.*

improvement in placebo patients, but the difference was not statistically significant ($P < 0.07$). A Level 1 study did not find significant effects of intralesional verapamil on penile curvature deformity, plaque size, or penile pain compared with saline injection [31]. Intralesional nicardipine injection, a calcium antagonist alternative to verapamil, resulted in reduced plaque size and penile pain compared with placebo (Level 1 study). However, decreased penile curvature deformity did not differ between nicardipine and placebo patients [32].

Intralesional IFN α-2b, 5×10^6 U administered every other week for 12 weeks, resulted in significantly greater improvement in penile curvature deformity and plaque size and density, as well as resolution of penile pain, compared with saline placebo (Level 1 study) [34]. Additionally, the treatment group showed significantly decreased penile vascular pathologies, important for its association with reduced ED, whereas the placebo group showed a deterioration trend [34]. In a partial crossover study (Level 2 study), treatment was associated with an average 25% improvement in penile angulation and reduced penile pain in eight of 10 men [35]. A Level 2 pilot study found improved penile curvature deformity of an average 20° in six of 10 patients who received IFN α-2b [36].

After CCH treatment (Level 2 study), a significantly greater percentage of patients (36%) showed a positive response in penile curvature deformity or plaque size or number compared with saline placebo (4%, $P < 0.007$) [37]. Greater treatment response was found in patients with penile curvature deformity of ≤60° and/or ≤4 cm palpable plaque compared with patients with penile curvature deformity of >60° and/or plaque >4 cm. A phase 2b double-blind RCT (Level 1 study) found CCH-treated patients showed significant improvement in penile curvature deformity (29.7% vs 11.0%, $P = 0.001$) and symptom bother scores on the PD-specific patient-reported outcome questionnaire compared with placebo ($P = 0.05$) [39]. The most rigorous CCH treatment trial to date includes two phase 3 double-blind RCTs involving 832 patients from 64 sites across the USA and Australia treated and followed over 52 weeks (Level 1 study) [40]. CCH-treated patients showed a mean 34% improvement (mean [SD] −17.0° [14.8] ° change per subject) in penile curvature deformity compared with 18.2% improvement (mean [SD] −9.3° [13.6] ° change per subject) in placebo-treated patients ($P < 0.001$). Additionally, the mean (SD) change in PD symptom bother score was significantly improved in CCH-treated patients (−2.8 [3.8]) vs placebo (−1.8 [3.5], $P = 0.004$). Overall, studies have generally found mean improvements in penile curvature of 15–20° with CCH treatment [37,39,40].

Discussion

A key benefit of evidence-based, minimally invasive treatment is that the improvement of PD symptoms can be achieved with less treatment-related morbidity than occurs with surgery. However, for most historically available therapies, trials have not shown consistent results and often there is a lack of empirical support for effectiveness [11,19,43]. Additionally, study designs are frequently compromised by the absence of a placebo/control group, which is especially important given the variable disease course of PD, as well as few patients, short duration follow-up, and the lack of consistent, objective measurements of change [43]. Critical analysis of empirical support using levels of evidence is needed to identify and separate potentially effective minimally invasive treatments from those with no evidence-based support. The present review used more rigorous evidence-based criteria to select studies compared with other recent reviews of minimally invasive treatments [11,44–46]. This approach allows the subset of treatments with the strongest support to be identified, with the corollary limitation that several studies that do not meet these criteria are excluded. RCTs were examined to determine the evidence base for minimally invasive PD treatments with a particular focus

on improvement in penile curvature deformity. All of the reviewed studies were randomised and placebo-controlled and used objective and standard accepted outcome measures for assessing penile curvature deformity. Level 1 studies included larger patient numbers (>50), were either single- or double-blinded, and examined longer-term outcomes (≥3 months). Level 2 studies did not meet one or more of the Level 1 study criteria.

Studies to date indicate improvement of penile curvature deformity in patients with PD after treatment compared with placebo-control for intralesional injection therapy with IFN α-2b (one Level 1 study and two Level 2 studies) and intralesional injection therapy with CCH (two Level 1 studies and one Level 2 study) [34–37,39,40]. An important goal for future studies is the continued evaluation of the clinical meaningfulness of the demonstrated improvement in penile curvature deformity after intralesional IFN α-2b and CCH treatment over a more prolonged follow-up period. The present review is consistent with recent PD treatment guideline recommendations supporting the effectiveness of intralesional IFN α-2b and CCH therapy in the reduction of penile curvature deformity and extends the support for CCH treatment by inclusion of recently published phase 2b and phase 3 placebo-controlled studies [11,34–37,39,40,44].

Among the remaining minimally invasive treatments, topical treatment with verapamil, oral treatment with vitamin E, carnitine, colchicine, the PDE manipulator pentoxifylline, or PDE5 inhibitors, and penile traction therapy could not be reviewed as no placebo-controlled trials have been reported. Consistent with the treatment guidelines by Ralph et al. [11], topical treatment with verapamil is not recommended due to the demonstrated inability of topical verapamil to penetrate the tunica albuginea [11,14]. Further, consistent with the treatment recommendations of Ralph et al. [11] and Hatzimouratidis et al. [44], treatment with corticosteroids is not recommended due to lack of evidence-based effectiveness and the potential for serious adverse events [11,19,44]. Due to the lack of placebo-controlled studies, many of the oral treatments were not included in the present review; however, these treatments (i.e. vitamin E, tamoxifen, carnitine, pentoxifylline, colchicine) are currently not recommended in PD treatment guidelines due to lack of support for effectiveness in reduction of penile deformity in less methodologically rigorous studies [11,44].

Minimally invasive therapies that have shown mixed or negative results in Level 1 or Level 2 RCTs include oral therapies (Potaba, tamoxifen), ESWT (one Level 1 study and one Level 2 study), EMDA (three Level 2 studies), and intralesional injection with verapamil (one Level 1 study and one Level 2 study) or nicardipine (one Level 1 study). No significant difference between treatment and placebo groups in improved penile curvature was found in two studies of ESWT [26,27]. However, one of the studies suggested the treatment group showed less worsening (or, greater stability) of penile curvature over 6 months compared with the progressive worsening of penile curvature that occurred in the patients in the placebo group [26]. Among three EMDA studies, two showed significantly reduced penile curvature in the treatment group compared with placebo [28,29,41]. However, one of these positive studies used 2% lidocaine as the placebo [29], and it has been suggested that lidocaine may stabilise membranes and decrease potential PD improvement leading to the false appearance of a treatment effect [28]. Neither of two studies examining intralesional injection with verapamil found significantly decreased penile curvature compared with placebo, although one of the studies showed a trend in treatment effect [13,31]. The single placebo-controlled study that examined intralesional injection of nicardipine did not find a significant improvement in penile curvature. Among the available minimally invasive treatments, Potaba, intralesional injection with verapamil, EMDA/iontophoresis, and penile traction devices have been included in PD treatment guideline recommendations citing possible effects on stabilising or improving penile curvature as shown in studies using less rigorous methodology than were included in the present review [11,44]. From the perspective of the present review, additional Level 1 or Level 2 studies that consistently show significant improvement of penile curvature deformity compared with a placebo control are needed before these treatments can be unequivocally recommended as evidence-based.

Conclusions

PD is a challenging disorder to manage. Effective minimally invasive treatment options are highly desired by patients as an alternative to surgery because of the treatment-related morbidity associated with surgery. The minimally invasive treatments with the highest level of evidence supporting effectiveness in improvement of penile curvature deformity include intralesional injections using IFN α-2b or CCH. Recognition of PD and initiation of an evidence-based minimally invasive treatment are both key to improving patient outcomes.

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Conflict of Interest

G.H.J. is an investigator for Auxilium, a consultant for PNN Medical, and a scientific board member for Precision Medical Devices. C.C.C. is a consultant and speaker for American Medical Systems, Auxilium, GlaxoSmithKline, and Lilly. L.I.L. is a consultant, speaker, advisor, and investigator for Eli Lilly; a speaker for Endo and Auxilium; and a meeting participant and speaker for Pfizer and American Medical Systems. He also participated in clinical trials for Auxilium, Lilly, Endo, and Allergan.

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Abbreviations: CCH, collagenase clostridium histolyticum; ED, erectile dysfunction; EMDA, electromotive drug administration; ESWT, extracorporeal shockwave therapy; IFN, interferon; MeSH, Medical Subject Headings; PD, Peyronie's disease; PDE, phosphodiesterase; PDE5, phosphodiesterase-5; Potaba, potassium para-aminobenzoate; RCT, randomised, placebo-controlled trial.