Recent advances in managing Peyronie’s disease [version 1; peer review: 2 approved]

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Abstract
Treating men with Peyronie’s disease remains a challenging problem facing clinicians working across urology and sexual medicine fields. Patients can often be left disappointed by current treatment paradigms, and an overall lack of suitable molecular targets has limited the options for novel, effective medical therapy. Managing men with Peyronie’s disease often involves careful counselling alongside multifaceted and possible combination treatments to help improve symptoms whilst ameliorating potential side effects of therapy. We review the latest medical literature and evidence in the contemporary management of Peyronie’s disease.

Keywords
Peyronie, collagenase, traction therapy, fibrosis, treatment, Peyronie’s disease, urology, erectile dysfunction, non-surgical treatment
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Background

Peyronie’s disease (PD) is a relatively common progressive fibrotic disorder that affects the tunica albuginea. Traditionally, men will present with a new penile curvature, which may be associated with pain in the acute phase. Prevalence is reported to be in the region of 0.4–20%, with manifestation typically in the fifth decade of life1–3. PD may also be frequently associated with erectile dysfunction, penile shortening, psychological distress, and a palpable plaque, which is typically found on the dorsal aspect of the penile shaft. In some men, the penile curvature is severe enough to impair penetrative sexual intercourse.

The natural history of PD is divided into the active and quiescent (chronic or stable) phases. During the active phase, patients may report penile pain with a changing deformity (1–6 months). In contrast, the stable phase is generally associated with a painless and stable penile deformity (6–18 months).

Observational studies have shown that the majority of patients with PD will eventually have a stable curvature (40–47%), with a similar proportion showing progression (40–48%) and a much smaller group spontaneously improving (12–13%)4,5. PD affects men principally between the ages of 40 and 60 and is associated with diabetes mellitus, Dupuytren’s contracture, and plantar fascial contracture (Ledderhose disease). There may be a preceding history of trauma.

The most common hypothesis regarding aetiology of the disease involves repeated minor microvascular trauma during intercourse resulting in intratunical bleeding and subsequent inflammation and fibrosis. Interestingly, we have seen PD in sexually naïve men who have never had penetrative intercourse. This may not refute the hypothesis but points further to a multifactorial process. Transforming growth factor beta (TGF-β) is thought to exacerbate the erratic healing response. Histologically, there is excessive connective tissue, increased cellularity, and random orientation of collagen fibres within the Peyronie’s plaque. Subsequently, the dysfunctional tunical tissue restricts normal expansion of the underlying corpus cavernosum, creating the observed curvature. There may be flaccidity distal to the lesion with or without a waisting (hourglass) deformity or rotation observed in more severe cases.

Surgical correction has historically been the mainstay of treatment but can harbour significant morbidity and in some series is related to poorer patient-reported outcomes. Patient morbidity from surgery includes haematoma and infection in the early post-operative period, with penile shortening, recurrent/residual curvature, glans hypoesthesia, and delayed erectile dysfunction manifesting later. In the majority of published case series, the main reasons for poor patient-reported outcomes tend to relate to the presence of residual curvature, overt penile shortening, and erectile dysfunction, with dissatisfaction rates ranging from 27–45% in those undergoing plication or plaque excision and grafting6. As a result of this, there has been extensive research into non-surgical interventions that can potentially stabilise or improve penile curvature without the morbidity associated with surgery.

The aim of this review is to summarise the most recent advances in PD treatments, including surgical techniques, non-surgical interventions, and basic science updates. A review of the literature from 2017 onwards (24 months) was conducted by performing a MEDLINE® search of publications using the keyword “Peyronie”. In the absence of any new data for specific treatments or to consolidate the evidence around newer therapies, we have included older key papers for the readership’s general information.

Basic science

The most accepted pathophysiological aetiology of PD is that of microtrauma. This results from repeated injury resulting in an inflammatory response that promotes the formation of fibrous plaques through mediators such as TGF-β. There are very few studies that are able to show a clear correlation between the histological findings of trauma and Peyronie’s plaques in human histological specimens6,7. El-Sakka et al. verified that TGF-β is strongly expressed in PD histology in a rat model, leading to an inflammatory process and fibrosis8. De Rose et al. conducted a prospective observational study comparing the histological and ultrastructural changes seen in patients undergoing plaque excision for PD (in the absence of trauma) and those undergoing plaque excision for a history of penile fracture. The results showed the two groups had very similar collagen deposition, cellular composition, and extracellular matrix, in keeping with the proposed aetiology of microtrauma being the underlying cause of PD9.

Stem cell therapy

Stem cells are undifferentiated cells that are capable of self-renewal and differentiation, promoting the repair of tissues via their immunomodulatory and anti-inflammatory action. Adipose-derived stem cells (ADSCs) are used most widely owing to their abundant tissue source and ease of isolation. There is currently limited evidence for the clinical use of stem cells in PD, with all studies restricted to rat models. Milenkovic, Albersen, and Castiglione reviewed the current evidence, which was limited to only four pre-clinical studies using ADSCs10. Overall, these data support positive effects through differing proposed mechanisms of action, including reducing collagen and elastin deposition, reducing fibrosis, and increasing myofibroblast apoptosis11–15. Further clinical studies are needed to confirm the efficacy of stem cell therapy for PD in humans.

Pharmacotherapy

No oral pharmacotherapy is recommended by the American Urological Association (AUA) or the International Consortium of Sexual Medicine (ICSM) because of the lack of robust evidence. In contrast, the European Association of Urology (EAU) suggest that potassium para-aminobenzoate (Potaba) may result in a significant reduction in curvature, plaque size, and pain16–19. Generally, the EAU, AUA, and ICSM guidelines have similar recommendations but differ on a few key points. These comparative points are highlighted in Table 1. Unfortunately, it is beyond the scope of this review to further delineate any methodological or reporting differences used between these different...
guidelines panels that might generate further discussion regarding monotherapy or combination treatments. Suffice to say, given the relative paucity of high-quality evidence in this area, it is reasonable to concur that current oral monotherapies are universally considered to be of limited clinical use as a medical tool to directly reverse or modify PD outcomes in patients, either for symptom relief or to modify or improve longer-term functional outcomes.

Potaba
Two placebo-controlled randomised controlled studies (RCTs) have shown evidence that Potaba may reduce progression and pain\(^{20,21}\). Weidner \textit{et al.} demonstrated that penile plaque size was stabilised in the Potaba group compared to placebo. This subsequently reduced the progression of curvature in the treatment group when compared to placebo; however, it did not reduce any established curvature. This group did not demonstrate any evidence of improvement in pain relief. This is in contrast to the earlier RCT by Shah \textit{et al.}, which demonstrated no evidence of improvement in curvature/plaque; however, it did show there was some improvement with regard to pain. Based on these two RCTs, Potaba currently is the only oral medication that has any recommendation for use within the EAU guidelines.

More recently, Potaba monotherapy was compared to combination therapy (tamoxifen, L-carnitine, and tadalafil) by Park \textit{et al.}\(^{22}\). Perhaps the most striking result was that two-thirds of the patients in the Potaba arm withdrew for various reasons, although treatment side effects were cited as the largest single factor. The study failed to show any statistically significant difference between the two treatment arms owing to the high dropout rate. Overall, the most clinically relevant conclusions from this study showed that the side effect profile of Potaba may lead to very poor compliance and a high discontinuation rate.

The potential adverse effects of treatment alongside the limited evidence of efficacy therefore limit the recommendation of Potaba use, which is why it is not recommended by the AUA or ICSM at the time of writing.

Vitamin E and antioxidant therapy
Vitamin E is a fat-soluble, naturally occurring antioxidant that has previously been shown to improve pain, curvature, and erectile function scores (IIEF) and has been utilised in combination therapy with verapamil injections, non-steroidal anti-inflammatory drug, PD, Peyronie's disease; Potaba, potassium para-aminobenzoate.

Table 1. Non-operative management of PD: summary of EAU, AUA, and ICSM guidelines\(^{17-19}\).

| Therapy                  | EAU (2015) | AUA (2015) | ICSM (2016) |
|--------------------------|------------|------------|-------------|
|                          | Advised    | Not advised| LoE         |
| NSAID                    | -          | ✓          | -           |
| Potaba                   | ✓          | C          | x           | x           | B           |
| Vitamin E                | x          | B          | x           | B           | x           | B           |
| Tamoxifen                | x          | B          | x           | B           | x           | B           |
| Carnitine                | x          | C          | x           | B           | x           | B           |
| Pentoxifylline           | x          | C          | x           | B           | x           | B           |
| Colchicine               | x          | C          | x           | B           | -           |
| Collagenase (I/L)        | ✓          | B          | ✓           | B           | ✓           | B           |
| Verapamil (I/L)          | ✓          | C          | ✓           | C           | ✓           | C           |
| Interferon (I/L)         | ✓          | C          | ✓           | C           | ✓           | B           |
| Steroids (I/L)           | x          | B          | x           | -           | x           |
| Verapamil gel            | ✓          | C          | x           | x           | B           |
| Verapamil and steroids (I/O) | ✓      | C          | x           | -           | x           | B           |
| ESWT                     | ✓          | ✓          | ✓           | ✓           | ✓           | C           |
| Mechanical               | ✓          | C          | x           | -           | ✓           |

AUA, American Urological Association; EAU, European Association of Urology; ESWT, extracorporeal shockwave therapy; ICSM, International Consortium of Sexual Medicine; I/L, intralesional; I/O, iontophoresis; LoE, level of evidence; NSAID, non-steroidal anti-inflammatory drug; PD, Peyronie’s disease; Potaba, potassium para-aminobenzoate.
diclofenac, and pentoxifylline injections. Throughout all groups, there was prevention in progression of disease. As the number of treatments increased, there was an improved outcome, particularly in IIEF score, reduced curvature, and improved quality of life/bother scores. The curvature improvement was minimal (4–6°) and likely clinically insignificant. In view of the study design not being randomised or controlled, the results must obviously be taken with caution25.

**Phosphodiesterase-5 inhibitors and tamoxifen**

A recent scientific study has investigated a new model to test potential medical therapies in PD. The team describe an *in vitro* model that mimics the cellular changes seen in PD. It is well understood that myofibroblasts play a large role in the remodelling of the extracellular matrix and the production of profibrotic mediators and inflammatory cytokines26,27. These cell lines have also been isolated in PD plaques28. The authors were able to create a screening assay to assess the effectiveness of multiple treatments on the transformation of fibroblasts to myofibroblasts. Using this innovative model, they assessed the efficacy of 21 commonly studied oral therapies. The only compounds that proved to be effective on the fibroblast model included phosphodiesterase (PDE)-5 inhibitors and tamoxifen. These medications were then tested further in separate testing systems. The authors noted that each medication has the potential to prevent progression of disease in the active phase but is unlikely to reduce the plaque or curvature. They also identified that there was a synergistic effect with the two medications combined compared to either medication alone29.

**Pentoxifylline**

Pentoxifylline is a non-specific PDE inhibitor that also has some effect in reducing TGF-β tissue levels and therefore may have an antifibrotic role and thereby a therapeutic role in PD30. The evidence of its efficacy is limited as a monotherapy; however, there is some evidence to suggest its benefit as a combination treatment.

Smith *et al.* investigated the effect of pentoxifylline monotherapy on plaque calcification and subjective improvement of the clinical condition. They studied 71 men in a cohort study, of whom 62 were treated with pentoxifylline and nine received no treatment. The study showed that 92% of patients treated with pentoxifylline compared to 44% with no treatment had stable or improved plaque calcification. There were no objective outcomes to suggest improvement in curvature; however, there was subjective patient-reported improvement, which makes it somewhat difficult to make any firm conclusions regarding its true clinical benefit31.

A further cohort study conducted by Alizadeh *et al.* compared pentoxifylline with intralesional verapamil and a combination of both therapies. A total of 90 patients were enrolled into three treatment arms (n = 30) with no control group. They reported improvement in curvature, plaque size, pain, and erectile dysfunction in all groups. Outcome measures were not quantitative and therefore no conclusions about degree of curvature change can be made32. Recently, an older double blind RCT conducted by Safarinejad in 2010 using pentoxifylline monotherapy has since been redacted because of statistical incongruities33.

A study exploring pentoxifylline as part of a combination therapy has been recently completed by Ibrahim *et al.*34; a total of 46 patients were included in this retrospective cohort study, which aimed to assess the effect of colchicine or pentoxifylline with penile traction therapy (PTT) (Andropenis® extender) on plaque size, degree of curvature, and penile Doppler parameters. Patients were assigned to oral pentoxifylline (n = 27) and colchicine (n = 18) with all advised to use PTT for 1 hour daily for a total of 6 months. The study reported an improvement in curvature of 14° (55.8° versus 41.4°) and also reported improvement in peak systolic velocity and reduction in plaque size. They found no statistically significant difference in the colchicine or pentoxifylline arm. The study has significant limitations in that there was no control group; therefore, it is possible that the improvement may have been purely spontaneous. It must also be noted that all patients received PTT, which potentially could explain why these parameters improved rather than as a result of any efficacy from the oral therapies. The efficacy of the Andropenis® extender is discussed further in this paper.

**Intralesional injection therapy**

**Collagenase**

Collagenase clostridium histolyticum (CCH) has been studied for use in PD in the experimental field since 1982. Since 2013, CCH has been approved by the United States Food and Drug Administration as well as the European Medicines Agency. Treatment comes in the form of an injection of two collagenases, which act synergistically to cleave tropocollagen. Its use is recommended by the AUA for PD curvature between 30° and 90°, and the EAU guidelines currently advise a grade B recommendation; however, these guidelines precede the largest published RCT37.

IMPRESS I and II were large RCTs comparing CCH and penile modelling against penile modelling and placebo with 417 and 415 patients included in the study, respectively. Exclusion criteria included any patients with an hourglass deformity, significant erectile dysfunction non-responsive to PDE-5 inhibitors, proximal plaques, and curvature outside 30–90°. The treatment protocol involved two injections of CCH (0.58 mg) 24 to 72 hours apart. This cycle regimen was then repeated up to four times, alongside penile modelling by the clinician at the time of injection as well as by the patient three times daily thereafter until review. Curvature improved by 17° and 9° (34% versus 18.2%) in the treatment and placebo arms, respectively. There was also similar improvement in IIIEF scores (+1 and +0.4, respectively) as well as penile length (0.4 cm and 0.2 cm, respectively). PD questionnaire (PDQ) bother scores were also improved in the treatment group; however, one-third of the cohort did not complete the questionnaire at one or both measurement points, and the PDQ is still not validated psychometrically38,39.

Ralph *et al.* conducted a randomised study comparing CCH, modelling, and vacuum therapy to CCH and vacuum therapy alone. This small pilot study (n = 30) did not show any statistically significant difference between the two groups in terms of
curvature improvement or patient-reported outcome measures. There was a clear improvement in curvature of 23.7° in the CCH, modelling, and vacuum therapy group compared to 23.3° in the group without penile modelling. The injection protocol was similar to that in the IMPRESS trial with the addition of vacuum therapy being initiated following the second injection twice daily throughout the remainder of the study. There was only clinician modelling performed, with no patient modelling performed in either arm of the study.\(^\text{36,37}\)

A further study by this same group explored a modified injection protocol in a single-centre study of 53 patients alongside vacuum therapy during remodelling. The injection protocol consisted of three injections of 0.9 mg of CCH every 4 weeks. This was accompanied by manual modelling as well as vacuum therapy, and results showed equivalent outcomes to the IMPRESS trial with mean reduction in curvature of 17.3° (31.4%). This treatment regime reduced the need for multiple visits for injections and clinician modelling, which has the potential to lower costs and time for treatment\(^\text{37}\). More recently, Capece and colleagues used the modified injection and remodelling protocol to perform a non-randomised, non-controlled multicentre study of 135 patients. They were able to reproduce the efficacy as described previously, with a mean reduction in curvature of 19° (42%). They did, however, note a slightly higher complication rate in the form of ecchymosis and haematoma when compared to the IMPRESS trial\(^\text{38}\).

Ziegelmann et al. compared CCH and PTT versus CCH alone using a similar injection protocol to the IMPRESS trial with the addition of PTT for 3 hours per day. They found no significant difference in outcomes for CCH alone versus CCH and concomitant PTT. Overall curvature improvement was similar to that of the IMPRESS study, with a mean of 34% improvement. They reported poor adherence to the traction therapy with reduced compliance throughout the study, therefore likely limiting its effect. Ultimately, the authors felt that further RCT studies will be required to determine the role of traction therapy with CCH\(^\text{39}\).

The latest published study in CCH treatment from an Italian group demonstrates a matched-pair comparison analysis of CCH in combination with sildenafil during the modelling phase. Using the same injection protocol as described in their previous study, they added sildenafil 25 mg BD 30–60 minutes prior to patient modelling. This was a small cohort study of 50 patients comparing the modified CCH protocol against CCH with the addition of sildenafil. They were able to show improved outcomes in curvature, IIEF scores, and PDQ scores, which were deemed to be statistically significant; however, the overall cohort was small. Curvature was improved by 25.6° in the CCH + sildenafil group compared to 17.4° in the group given CCH alone. This is clearly a promising outcome but needs further study in larger RCTs prior to any firm conclusions or recommendations being made\(^\text{40}\).

CCH has clear robust RCT data showing definitive benefit in patients with PD and a penile curvature between 30° and 90°. There are numerous single-arm studies assessing variable treatment protocols that suggest that dosing adjustments can be made with associated accelerated treatment times and cost savings without compromising outcomes or safety parameters. It must also be noted that the IMPRESS studies showed a clear curvature improvement in the penile modelling group that is likely greater than placebo alone; this indicates that mechanical/modelling therapies alone may well have some efficacy, as outlined later in this article.

CCH clearly offers a less-invasive approach when compared to surgery; however, it is clear that the degree of curvature improvement is not as significant as is seen with surgery. Nevertheless, it does offer a treatment option for a select group of patients who may not be amenable to surgical intervention and would prefer conservative treatment if possible. The ‘real world’ paper by Anaissie et al. succinctly concluded that ultimately CCH needs further study to understand the optimal patient and which treatment regime produces the most efficacious result in terms of curvature improvement without being prohibitive on cost\(^\text{37}\). We therefore eagerly await the results of larger, multicentre, and randomised studies to further focus on predictive factors for treatment success or failure and provide guidance for implementing CCH treatments in socially funded healthcare systems.

The most recent unexpected update regarding CCH is its untimely removal from the European market by the manufacturers. This is an evolving situation, and the authors hope that an alternative product will be available in the near future\(^\text{41}\). A summary of the salient studies and most recent clinical evidence in CCH can be found in Table 2.

**Verapamil**

Intralesional verapamil injections are within the recommendations for treatment in the EUA, AUA, and ICSM guidelines. However, their use is supported by overall poor evidence and hence is given a grade C recommendation by all guidelines\(^\text{37–39}\).

Verapamil is a calcium channel blocker that has been shown to interfere with fibroblast proliferation and can decrease collagen deposition by upgrading collagenase activity. There are only two trials comparing verapamil treatment and control subjects.

Rehman et al. produced a small randomised control study comparing intralesional verapamil injections against placebo in a group of 14 patients. They used 10–27 mg injections weekly for 6 months. They were able to show a reduction in plaque length, curvature (7.9° in the treatment group compared to 2.2° in the placebo group), and penile pain\(^\text{42}\). A further RCT by Shirazi et al. compared 10 mg verapamil injections to placebo. A total of 80 patients were enrolled and randomised 1:1 to either the treatment or the placebo arm. In the treatment group, patients were given 10 mg injections twice weekly for a total of 12 weeks. In contradiction to Rehman et al., they were unable to find any significant improvement in curvature, plaque size, or penile pain reduction when compared to placebo\(^\text{43}\).

Favilla et al. recently compared intralesional injections of verapamil against hyaluronic acid (HA) in a double blinded randomised study. A total of 132 patients were included and
given either weekly 10 mg intralesional verapamil or 16 mg/2 ml injections of HA. Outcomes showed a statistically significant improvement in plaque size (–1.36 mm and –1.8 mm) and IIEF score (1.46 and 1.78) in the verapamil and HA group, respectively. There was no improvement in curvature in the verapamil group in comparison to the HA group, which improved by 4.6°.

There have been a number of further comparative randomised studies of verapamil over the past 10 years that have significant heterogeneity in their treatment regimens and also their comparative treatments. Greenfield et al. compared verapamil with saline in electromotive drug administration (EMDA) for PD. This study failed to show any statistically significant improvement in curvature. A randomised trial by Mehrsai et al. compared treatment in 60 patients treated with verapamil either via injection or EMDA. The authors found no significant difference in reduction of plaque size; however, they did note an improvement in erectile function (albeit not significant). Penile pain assessed by visual analogue scale was significantly reduced in the EMDA group compared with the injection group (–4.1 versus –1.8) at 3 months. Penile curvature was improved in both groups, and increased shift towards a ‘less-than-30°’ group was noted especially in the EMDA category. This improvement, however, was not quantified in more detail or statistically significant.

Abern et al. compared verapamil, oral pentoxifylline, and L-arginine (group 1) against the same medical therapy and additional PTT (group 2). Both groups had improved penile curvature, and interestingly the PTT group (group 2) had less curvature improvement (11°) when compared to medical therapy and injections alone (15.1°). The authors did not complete any statistical comparison between the two groups.

### Table 2. Summary of evidence showing the efficacy of CCH.

| Author            | Year of study | Aim of study                                      | Type of study | No. of patients | Injection protocol | Adjunct                       | Follow-up (weeks) | Curvature improvement |
|-------------------|---------------|---------------------------------------------------|---------------|-----------------|-------------------|-------------------------------|------------------|-----------------------|
| Gelbard et al.    | 2013          | To assess efficacy of CCH alongside penile modelling | RCT           | 832             | Two 0.58 mg injections, 24–72 hours apart Up to eight injections total | Clinician penile modelling | 52                | 17°                   |
| Levine et al.     | 2015          | To assess efficacy of CCH alongside penile modelling | Phase III open label | 347             | Two 0.58 mg injections, 24–72 hours apart Up to eight injections total | Clinician penile modelling | 36                | 18.3°                 |
| Ralph et al.      | 2017          | Assess efficacy of CCH + vacuum therapy +/- penile modelling | Randomised pilot | 30              | Two 0.58 mg injections, 24–72 hours apart Up to eight injections total | Vacuum therapy +/- penile modelling | 36                | 23.7° in CCH + vacuum therapy + modelling 23.3° in CCH + vacuum therapy |
| Abdel Raheem et al. | 2017       | To assess the safety and efficacy of modified injection protocol | Pilot          | 53              | Three 0.9 mg injections 4 weeks apart | Patient modelling and vacuum therapy | 12                | 17°                   |
| Ziegelmann et al. | 2017          | To compare efficacy of CCH + traction therapy against CCH alone | Prospective, non-randomised, non-controlled | 51              | Two 0.58 mg injections, 24–72 hours apart Up to eight injections total | Penile traction 3 hours daily + penile modelling | 24                | 19.6° in CCH and traction 23.6° in CCH alone |
| Capece et al.     | 2018          | To assess efficacy of modified protocol            | Multicentre, non-randomised, non-controlled prospective | 135             | Three 0.9 mg injections 4 weeks apart | Patient modelling and vacuum therapy | 12                | 19°                   |
| Cocci et al.      | 2018          | To assess the efficacy of CCH + sildenafil         | Prospective, non-randomised, non-controlled matched-pair comparison | 50              | Three 0.9 mg injections 4 weeks apart | Sildenafil 25 mg twice daily prior to patient modelling + vacuum therapy | 12                | 25.6° in CCH + sildenafil 17.4° in CCH alone |

CCH, collagenase clostridium histolyticum; RCT, randomised controlled trial.
Interferon α-2B

There have been no recent randomised placebo-controlled studies using interferon (IFN) α-2B. Kendirci et al. and Hellstrom et al. produced two placebo-controlled studies in 2005 and 2006, respectively. Kendirci et al. randomised 5 × 10⁵ IU of IFN against placebo with a total of six injections given once weekly. They showed a statistically significant improvement in penile curvature with IFN of 12° compared to 3.6° in the placebo group. Hellstrom et al. produced similar results to Kendirci with a similar improvement in curvature.²⁵,²⁶

More recently, Yafi et al. compared IFN with PTT versus IFN alone. This retrospective study had no placebo arm but did show a marginal improvement in curvature of 8.1° in the IFN and traction group compared to 9.9° in the IFN group, respectively. This difference in outcomes between groups was not statistically significant²⁷.

The most recent publication regarding IFN injection therapy was a single-arm prospective non-randomised study performed by Sokhal et al. including 86 patients receiving 3 × 10⁶ IU of IFN once weekly for a 12-week period. Follow-up was limited to only 3 months; however, there was a statistically significant improvement in plaque size, curvature, and IIEF-5 and pain scores. Plaque length reduced from 12.9 mm to 4.3 mm, and curvature improved by 16.2° (34.8° reduced to 18.6°) over the 3-month treatment period.²⁸

Hyaluronic acid

Gennaro and colleagues conducted a prospective RCT comparing intraleisional HA compared with placebo in 2012. This study comprised 86 patients, with the treatment arm undergoing a total of 30 HA (20 mg) injections over 6 months every 5–7 days. There was a curvature of improvement in plaque size, curvature, and IIEF when compared to placebo. At 24 months, the curvature was improved by 47% in the treatment arm, which equated to 9°. In the placebo arm, there was a deterioration in curvature of 19° over the same follow-up period.²⁹

A single-arm, multicentre, pilot study was published by Zucchi et al. in 2016 and reported on outcomes from a 10-week cycle of HA (16 mg) intraleisional injections in a total of 65 patients. They were able to demonstrate a statistically significant improvement in penile plaque length, curvature, IIEF, pain scores, and subjective outcome scores 2 months following the treatment regimen. Curvature was improved by 10° (from 30° to 20°) with no significant adverse events noted throughout the study.³⁰

The comparative study by Favilla et al. described previously in this paper also showed advantageous outcomes of HA when compared to verapamil therapy.³¹

Mechanical therapy for PD

Penile traction devices

Mechanical therapy for PD as a treatment modality generally suffers from a lack of robust, randomised controlled studies.³² The purported mechanism of action of traction devices is likely to be secondary to cellular mechanotransduction. The mechanical strain on the cell body leads to multiple signal transduction pathways being activated, which is likely to lead to collagen degradation.³³,³⁴ They currently have a grade C recommendation by the EAU and ICSM and are not recommended by the AUA owing to a lack of supportive evidence.³⁵,³⁶

Gontero et al. described a regime of increasing mechanical traction (Andropenis® extender) for a median of 5.5 hours a day over a 6-month period. They were able to produce a marginal non-statistically significant improvement of 4° from 31° to 27° following treatment. There was no improvement in IIEF or penile plaque length; however, there was a statistically significant improvement in stretched penile length of 0.8 cm.³⁷

Using the same device (Andropenis® extender), Martínez-Salamanca and colleagues studied its use in the acute phase of PD over a 6-month period. This prospective non-randomised study compared traction to a non-intervention arm involving patients also considered to be in the acute phase over a 9-month period. In the treatment arm, the prescribed therapy was use of the device for 9 hours per day; however, because of poor adherence, average compliance was 4.6 hours. In the treatment arm, there was a reduction from 33° to 13°, resulting in a 20° curvature improvement. In contrast, the non-intervention arm had worsening curvature over the follow-up period, increasing by 23°. Outcomes were also improved in stretched penile length and IIEF scores in the treatment arm. There was, however, no statistical analysis comparing the two arms of the study, and potentially it is likely that the non-intervention group may have been on several oral therapies for PD.³⁸

The first RCT of mechanical therapy has been published recently by Moncada et al. They conducted a study using the PeniMaster® PRO device compared to a control (non-intervention) group with promising results. A total of 93 patients were recruited and assigned to either arm of the study (47 in the treatment group and 46 controls). Follow-up was limited to 3 months, and treatment required use of the device for 3–8 hours daily. There was a clear reduction in penile curvature in the treatment group, which was directly correlated with adherence to device use. Overall reduction was significant at 31.2° (41.1%) compared to baseline, and there was no change in curvature in the control group. This reduction in curvature was enhanced when increasing the usage time. Greater than 6 hours’ use daily resulted in a 36.2° reduction compared to baseline (51.4%), whilst less than 4 hours produced a 19.7° improvement (28.8%). All of these results showed statistical significance. Furthermore, there was also increased stretched penile length and IIEF score. Outcomes are overall are promising; however, 43% of patients noted adverse events, which were mainly glans numbness/oedema and local irritation. A total of 6.5% of patients (n = 3) in the treatment arm abandoned the study owing to these adverse events.³⁹

More recently, Ziegelmann et al. published a further RCT using a novel mechanical device, RestoreX®. The newer device challenges some of the limitations seen with older, alternative traction devices, namely reduced usage times, increased comfort, and ability to bend the device to exert a focal, non-linear effect. The published trial studied 110 men using the device for only 30–90 minutes a day over a 3-month period. The study group was randomised 3:1 in favour of traction therapy. The results in
this trial showed significant promise considering the observed shorter treatment times. A reduction in curvature of 11.7°, improvement in penile length of 1.5 cm, and improvement in IIEF score by 4.3 points were demonstrated\(^6\). The control group showed no change in penile length, worsening IIEF, and an increase in curvature by 1.3°. Although this represents a relatively small study with short follow-up time, the results highlight potential positive efficacy and safety outcomes.

Alom et al. continued to study the benefits of the RestoreX® device alongside CCH injections\(^6\). They performed a comparative cohort study assessing three groups of therapy: CCH alone (group 1, \(n = 52\)), CCH plus other mechanical traction devices (group 2, \(n = 45\)), and CCH with RestoreX® device (group 3, \(n = 16\)). CCH protocol was the same across all patients and used the time schedule described in the IMPRESS trial. However, instead of two injections 24–72 hours per treatment, a single injection of 0.9 mg was used. Various mechanical devices were used in group 2, including the Andropenis® extender as well as the PeniMaster® PRO, which are described earlier in this review.

All of these alternative devices required treatment for over 3 hours per day; however, compliance was very poor, with only 16% of this group reaching the required treatment time (median 1.5 hours). In comparison, the RestoreX® group saw a treatment compliance of 97% (median 0.9 hours). The study highlighted an improvement in curvature, which was statistically significant in all groups. Group 1 were able to achieve a 16.5° improvement, group 2 a 20° improvement, and group 3 a 30° improvement. The RestoreX® group also showed a greater improvement in length and various subjective assessments (improved penetration, feeling of meaningful improvement, and estimated percentage improvement) when compared to the other two groups. Overall, the study was able to show the largest degree of curvature change in the literature when compared to any other adjunctive treatment with CCH. It must be noted that these outcomes need to be reproduced in a RCT and in a larger cohort using the RestoreX® treatment group.

The above trials on mechanical therapies have been tabularised in Table 3 with a brief outline of the clinical outcomes.

### Table 3. Summary of evidence showing the efficacy of mechanical therapies in PD.

| Author                  | Year of study | Aim of study                                                                 | Type of study                  | No. of patients | Device                                | Usage protocol                                      | Follow-up (weeks) | Curvature improvement |
|-------------------------|---------------|------------------------------------------------------------------------------|--------------------------------|-----------------|---------------------------------------|-----------------------------------------------------|-------------------|------------------------|
| Gontero et al.\(^{60}\) | 2009          | To assess efficacy of the Andropenis® extender for the treatment of PD      | Prospective, non-controlled   | 15              | Andropenis® extender device           | 5.5 hours daily for 6 months                        | 52                | 4°                     |
| Martínez-Salamanca et al.\(^{61}\) | 2014          | To assess efficacy of the Andropenis® extender for the treatment of PD in the acute phase | Prospective, controlled, non-randomised trial | 96              | Andropenis® extender device           | 6–9 hours daily for 6 months (4.6 hours/ daily actual compliance) | 24                | 20°                    |
| Moncada et al.\(^{62}\) | 2018          | To assess the efficacy of the PeniMaster® PRO for the treatment of PD       | RCT                            | 93              | PeniMaster® PRO                       | 3–8 hours daily for 3 months                        | 12                | Mean improvement: 31° >6 hours’ use; 36° <4 hours’ use: 20° |
| Ziegelmann et al.\(^{63}\) | 2019          | To assess the efficacy of the RestoreX® device for the treatment of PD      | RCT                            | 110             | RestoreX®                            | 30–90 minutes daily for 3 months                    | 12                | 11.7°                  |
| Alom et al.\(^{64}\) | 2019          | To assess the efficacy of CCH +/– traction therapy with either RestoreX® or other devices | Prospective comparative cohort study | 113             | RestoreX® or PeniMaster® PRO or Andropenis® extender | 30–90 minutes daily for RestoreX® >3 hours daily for other devices (actual use 1.5 hours) | 14                | Group 1 = 16.5° Group 2 = 20° Group 3 = 30° |

CCH, collagenase clostridium histolyticum; PD, Peyronie’s disease; RCT, randomised controlled trial
External shockwave therapy  
There has been limited research on external shockwave therapy (ESWT) for PD in recent times. Its use is not recommended by AUA, EAU, or ICSM guidelines for the treatment of curvature; however, it may have a use for those with penile pain secondary to PD\textsuperscript{[17–19]}. A recent meta-analysis by Gao et al. reviewed the most recent significant RCTs using ESWT for PD. They found no statistically significant difference in curvature; however, they did note a statistically significant improvement in pain scores as well as plaque size in the six studies included comprising 443 patients. The authors, however, did note that pain in PD is usually self-limiting, so the role of ESWT in reducing the pain in these patients is arguable\textsuperscript{[17]}.  

Of note, TachoSil®, which is a fibrin-coated collagen fleece, is becoming an increasingly studied graft material because of its surgical advantages (no requirement to suture graft material). Two comparative studies have reviewed TachoSil® and SIS in penile grafting procedures. Falcone et al. compared the graft materials after plaque incision during penile prosthesis implantation in 60 patients. They noted a reduced operative time in the TachoSil® group of 120 minutes compared to 145 minutes in the SIS cohort. There was no difference in functional outcomes or complication rate at 35 months between the two groups\textsuperscript{[66]}. Rosenhammer et al. produced a similar study with a matched-pair analysis to aid in comparative outcome measure. They retrospectively matched 43 patients who underwent penile plaque excision/incision and grafting using SIS with a prospectively collected cohort who had similar demographics and preoperative penile curvature undergoing the same procedure using TachoSil® as the graft material. Once again, operative times were significantly reduced in the TachoSil® group compared to SIS: 80 minutes and 104 minutes, respectively. The TachoSil® group also showed no evidence of recurrence compared to SIS (9%). Shortening was 28% in the SIS group compared to only 5% in the TachoSil® group, which was statistically significant. Complication rates were similar in both groups at under 10\%\textsuperscript{[70]}.  

Surgery  
Surgical techniques and outcomes  
There have been no significant advances in PD surgical management in terms of randomised controlled data. In keeping with historical trends, there have been numerous retrospective reviews of modifications to traditional plication and grafting techniques. Nevertheless, plication remains the standard of care for patients without erectile dysfunction and a curvature of less than 60° provided that the associated loss of length is not problematic. Incision and grafting are indicated in patients falling outside these criteria, although plaque excision without grafting has been reported previously as a simplified technique\textsuperscript{[65]}.  

Inflatable penile prosthesis (IPP) and manual remodelling have been re-assessed in a retrospective review by Chung et al. comparing choice of device manufacturer\textsuperscript{[59]}\textsuperscript{[2]}\textsuperscript{[2]}. They found high satisfaction (79%) and 5-year mechanical survival (87% or greater) in both AMS CX® and Coloplast Titan® devices as well as comparable revision and complication rates of below 10%. Further results regarding implant insertion and simultaneous plication demonstrated similar levels of satisfaction. Implant surgery remains the mainstay of treatment for patients with significant curvature and erectile dysfunction. Caution remains regarding a distinct lack of evidence to support universal surgical reconstruction in most men in order to provide safe and significant penile lengthening, as advocated by some surgeons globally.  

Graft materials  
Graft materials in those undergoing excision of the tunica albuginea in severe PD have been much debated and researched over recent years. The perfect graft material should be traction resistant, be easy to manipulate, and adhere to surrounding tissues with low risk of rejection. It should also be resistant to tension to prevent any aneurysmal dilation during normal erectile function. In addition, it should be economically viable and easily available. There has therefore been a large number of different grafting materials proposed and used in recent research for PD surgery including autografts, allografts, xenografts, and synthetics. Garcia-Gomez et al. recently reviewed the current evidence for all graft materials in tunica albuginea excision and grafting procedures. They concluded that the published series has significant heterogeneity in terms of patient selection, outcomes, and follow-up periods, therefore making definitive conclusions difficult. The authors did note that buccal mucosa, pericardium, porcine small intestinal submucosa (SIS), and TachoSil® are being used more extensively than most other materials, but unfortunately there is limited evidence to suggest one material over the other\textsuperscript{[65]}.  

Future studies and directions  
Over recent years, we have observed increasing interest and research into minimally invasive (or non-surgical) treatments for PD. The IMPRESS I and II studies have shaped the clinical landscape promoting the efficacy and safety of intralesional therapy using CCH alongside mechanical therapy devices. Accordingly, we have witnessed a rapid expansion in alternative therapeutic algorithms and improved understanding of the utility of CCH in certain men with PD. Future clinical research should continue to develop uniform research methodology and protocols, including a greater focus on patient-reported outcomes and cost-effectiveness analyses for newer treatments. Whilst multiple researchers have attempted to look into the efficacy of oral therapies for PD, we must concede that there is still no evidence to support their use as first-line treatments in either the acute or the chronic phases. We propose that developing better scientific models may translate into better drug screening and targeting opportunities to realise any meaningful future clinical outcome in RCTs or beyond. To better understand where PD lies among more systemic fibrotic conditions (e.g. normal/aberrant healing, retroperitoneal, liver, or lung fibrosis, etc.) requires careful collaborative efforts to share valuable clinical resources and data using ultimately expensive generated proteomic, genomic, and metabolomic data. This approach should focus on developing new biomarkers, compound screening, and application of improved imaging technology to effectively diagnose, prognose, and treat men with this debilitating heterogeneous and complex problem.
Currently, the future favours an expansion of intralesional CCH usage, becoming the mainstay of treatment for PD if costs and drug availability allow. This depends a lot on engagement from existing pharmaceutical partners, particularly whilst drug patents restrict competition in the open marketplace. There is no doubt that urologists around the world are motivated to help develop and deliver a portfolio of minimally invasive treatments for PD in order to prevent or prolong the time without surgical intervention. Reversing this paradigm will be challenging, but the stepping stones already exist with ‘hotspots’ of high-quality basic scientific and clinical research evidence that will shape future treatments for men with PD. This needs to be matched with an increased general awareness of the problem through public health channels and reflected in a better financial infrastructure to incentivise and reward high-quality research and clinical care.

Conclusions

Intralesional treatments with modelling are demonstrating notable promise in treating PD non-surgically and at an earlier stage in the disease process. Generally, high treatment costs in non-insurance-based health systems, diverse experience, and the lack of widespread availability impede the current evidence base, particularly in terms of randomised trials.

Whilst CCH outcomes and safety are supported by a large body of published evidence, the ideal treatment regime is still not clear, with a large number of studies being produced without control or comparative arms, thereby making the outcomes difficult to assess. IFN-α-2B is the only other injectable therapy worthy of mention at this stage. These studies show a small improvement in curvature with a smaller cohort of patients in comparison to IMPRESS I and II, and the results have not been reproduced for over 10 years. Unfortunately, there has been no further robust research in other injectable intralesional therapies, which will likely limit their translational use.

Penile traction and mechanical devices in PD are very likely to improve outcomes and may well have a further role in the primary treatment of PD or as an adjunct to injectable therapies. Newer penile traction devices show some promise, but further case-control studies will be needed to evaluate their potential as a non-surgical monotherapy.

Within surgery, there is interest in novel graft materials, and further study into these materials is certainly warranted. In particular, outcomes using TachoSil® when compared to the more commonly used SIS materials have generated interesting data with respect to benefits observed with intraoperative technique and functional outcomes; however, further long-term results and comparative studies are required.

Currently, we seek to develop improved tools to assess patient depression, systemic health issues, and markers of poor quality of life. PD remains a difficult condition to successfully treat and should remain the remit of dedicated sexual health specialists and surgeons if we are to improve outcomes for men affected by PD and their partners.

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   Competing Interests: This reviewer is associated with Endo Pharmaceuticals (maker of Xiaflex / CCH) - consultant, advisor, research funding and fellowship support.

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