



Non-conventional therapies for Peyronie's disease: what is the evidence for efficacy?

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Background: In recent years, there has been a surge in non-conventional therapies for Peyronie's disease (PD). With increasing interest in these novel therapies, we conducted a narrative review to explore the efficacy and safety of these treatments to provide clarity for patients and providers.

Methods: A literature search was conducted to find studies describing non-conventional treatments of PD. These treatments were defined as those within the standard of care, including intralesional therapies and surgical options.

Results: A total of 14 studies were found. Non-conventional therapies included platelet-rich plasma (PRP), hyaluronic acid (HA), combination therapy of PRP and HA, extracorporeal shockwave therapy (ESWT), stem cell therapy (SCT), mycophenolate mofetil (MMF), and H-100. Most studies were limited to animal models and reported modest improvements in angulation and erectile function. Complication rates and cost of each treatment were infrequently reported.

Conclusions: There is limited evidence supporting non-conventional therapies for PD. As such, they are currently not recommended in clinical guidelines.

Keywords: Peyronie's disease (PD); non-conventional therapy; erectile function; penile curvature

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Introduction

In recent years, several novel treatments for Peyronie's disease (PD) have emerged that are not part of current clinical guidelines (1-3). These non-conventional PD treatments include platelet-rich plasma (PRP), hyaluronic acid (HA), combination therapy of PRP and HA, extracorporeal shockwave therapy (ESWT), stem cell therapy (SCT), mycophenolate mofetil (MMF), and H-100. With the rapid expansion and interest in these novel therapies, it is important for both patients and providers to understand the latest evidence supporting their safety and efficacy. The purpose of this narrative review is to

analyze the current evidence supporting non-conventional treatments of PD.

Methods

A comprehensive literature search was conducted. Medline, Embase, Central, CINAHL, and Web of Science were searched to find studies published between January 2000 and January 2019 investigating current non-conventional treatments of PD. The following key terms were used: "Peyronie's Disease" OR "Penile Curvature," AND "Non-conventional treatment" OR "Platelet-rich plasma" OR "Hyaluronic Acid" OR "Extracorporeal Shockwave

Therapy” OR “Stem Cell Therapy” OR “Mycophenolate Mofetil” OR “H-100”. Review articles were excluded. Studies examining conventional treatments for PD were excluded. Our analysis focused on subjective and objective measures of improvement in angulation, erectile function, and pain. Complications and availability of each modality

were also compared.

Results

A total of 14 articles met the inclusion criteria for non-conventional therapies for PD (*Table 1*). These include PRP,

Table 1 Non-conventional therapies for Peyronie's disease

Treatment	Studies included	Efficacy (% of patients noticing improvement)	Degree of improvement (degrees in penile curvature corrected)	Complications	Availability
Platelet-rich plasma	Culha <i>et al.</i> (2019); Matz <i>et al.</i> (2018)	Animal models: 0% of mice exhibited improvement. No significant improvement in pathological examination of treated plaques; Patient outcomes: IIEF-5 scores improved by an average of 4.14 points (100% of PD patients; 12/12)	Not provided. 80% of patients reported subjective improvement in their degree of curvature	Not provided. Urethral bleeding (n=4)	A blood sample obtained from the patient being treated, easily available
Hyaluronic acid	Zucchi <i>et al.</i> (2016); Favilla <i>et al.</i> (2017)	Patient outcomes: 2 mm change in plaque size after treatment (P<0.0001); IIEF-5 score improved by 1 point (P<0.0001); VAS score improved from 6/10 to 8/10 on average; PGI-I questionnaire improved to 69%. Patient global impression of improvement (PGI-I) was found in the hyaluronic acid (HA) group compared to Verapamil (4.0 vs. 2.0; P<0.05)	Penile curvature changed by a mean of 10 degrees after treatment (P<0.0001). Penile curvature decreased 4.60 degrees (P<0.001)	None. None	Hyaluronic acid is abundant and accessible, provided in several sexual health clinics across North America
Shockwave therapy	Claro <i>et al.</i> (2004); Di Mauro <i>et al.</i> (2019)	Patient outcomes: 8 patients (32%) reported improvement in spontaneous erections; Penile plaque size improved from 1.78 to 1.53 cm ² ; penile length increased from 13.0 to 14.0 cm; Pain on VAS decreased from 7 to 3 on average; improvement in each of the IIEF sub-domains (P<0.001) and all three PD questionnaire domains (P<0.001) in a patient population of 325	Mean reduction of 21 degrees at 3 months (18/25 patients, 72%). Curvature improved from 30.4 to 25.0 degrees on average	Urethral bleeding (n=2). None	Shockwave therapy is accessible and provided in many sexual health clinics across North America
Combination hyaluronic acid and platelet rich plasma	Virag <i>et al.</i> (2017)	Patient outcomes: improvement in mean PDQ questionnaire in PDQ1 with P=0.002 (95% CI: 0.720; 2.968), PDQ2 with P=0.021 (95% CI: 0.275; 3.225) and PDQ3 with P<0.001 (95% CI: 1.520; 3.220). For patients with prior ED (n=11), observed a decrease in their deformation, improvement in erections, sexual activity improved. 73.3% of these ED patients demonstrated satisfactory results	Mean reduction of 18.08 degrees at 2 months	Ecchymosis was present in 16.7% of the patients and marked hematoma in 10%. Two patients suffered from transient hypotension after local anaesthesia	Not provided

Table 1 (*continued*)

Table 1 (continued)

Treatment	Studies included	Efficacy (% of patients noticing improvement)	Degree of improvement (degrees in penile curvature corrected)	Complications	Availability
Stem cell therapy	Ma <i>et al.</i> (2012); Castiglione <i>et al.</i> (2013); Gokce <i>et al.</i> (2014); Gocke <i>et al.</i> (2015); Levy <i>et al.</i> (2015)	Patient outcomes: Better preserved cavernosal function and erectile function with stem cell-seeded grafts in tunica albuginea reconstruction compared to graft alone; In PD patients, close to a 100% reduction in plaque volume at 6 months (10/10 plaques). No improvement in IIEF-5. Animal models: in rat models, decrease in fibrosis and elastosis. Increased collagen degradation via altered TIMPs and MMPs expression and activity. Improved erectile function	In one study, mean reduction of 49.7 degrees at 6 weeks	In one study, plaque development (n=1), priapism (n=1)	Adipose-derived stem cells are abundant and accessible. Avoids ethical and logistical issues with embryonic stem cells
Mycophenolate mofetil	Antoniassi <i>et al.</i> (2019)	Animal models: following 30 days of treatment in rats with TGF- β induced PD, the integrity of elastin and ratio of collagen type III/I were similar to control group	No significant improvement	None	Commercially available
H-100	Twindell and Levine (2016)	Patient outcomes: at 6 months, treated patients (n=11, with PD <12 months duration) reported a 22.6% increase in mean stretched penile length, 40.8% reduction in curvature, and 85.7% reduction in pain level	Mean reduction of 20.2 (range, 3–55) degrees at 6 months	Mild rash (n=3)	Components of H-100 are commercially available

IIEF, International Index of Erectile Function Questionnaire.

HA, combination therapy of PRP and HA, ESWT, SCT, MME, and H-100.

Platelet-rich plasma

PRP is a penile injection formed of various growth factors to facilitate tissue repair and wound healing. These factors include platelet-derived growth factor, transforming growth factor β (TGF- β), insulin-like growth factor, epidermal growth factor, and plasma proteins. PRP accelerates wound healing and tissue regeneration in affected regions. While it has been used in other surgical specialties and dental surgery, it is new in the treatment of PD.

In the histopathological examination of TGF- β induced Peyronie's plaques in rat models treated with PRP (n=20), Culha *et al.* reported similar fibrosis scores on H&E staining between the PRP-treated and untreated group (4 untreated *vs.* 3.4 \pm 0.5 treated, P=0.122) (4). Interestingly,

the PRP injection itself induced similar histological features as the Peyronie's plaque created by the TGF- β injection. Matz *et al.* investigated PRP injections in patients with PD (n=17), with a mean of 2.1 injections per patient (5). International Index of Erectile Function (IIEF) scores increased by an average of 4.14 points for all PD patients, with 80% achieving an improvement in erectile function.

However, the study by Matz *et al.* was non-randomized, retrospective, and lacked a placebo control group (5). The study is also limited by the small sample size. PRP requires injections to the penis, which is not only distressing to the patient but can result in fibrosis of the corpora cavernosa, further worsening the problem. The 2018 study by Culha *et al.* did not evaluate erectile capacities of the rat by measuring intracavernosal pressure, no staining was made with anti-TGF- β antigen, and a subjective scoring format was used instead of a quantitative method for studying fibrosis (4).

HA

HA is an extracellular matrix glycosaminoglycan that can support hydration and turgidity of the amorphous tissue matrix. In PD, HA is thought to oppose factors that promote inflammation and oxidative stress (6). A prospective, multi-center study by Zucchi *et al.* studied patients who received weekly intraplaque injections with HA (n=65) (7). At two months post-therapy, plaque size decreased by 2 mm, ($P<0.0001$), IIEF-5 scores improved by 1 point ($P<0.0001$), average visual analogue scale (VAS) score improved from 6/10 to 8/10, and patient global impression of improvement (PGI-I) scores improved by 69%. Penile curvature improved by an average of 10° (7). A 2017 double-blinded RCT involving men experiencing the acute phase of PD (n=132) comparing HA and verapamil demonstrated better PGI-I scores in the HA group (4.0 HA vs. 2.0 verapamil; $P<0.05$) and improvement in mean curvature by 4.60° ($P<0.001$) (8).

The study by Zucchi *et al.* lacked randomization and a placebo group, in addition to a limited sample size from each center (7). Furthermore, the VAS score was used to measure pain as opposed to standardized erectile questionnaires such as the IIEF. The 2017 study by Favilla is limited by the lack of a control group, short follow-up (12 weeks), and variability in plaque size measurement amongst the 11 centres (8). Although both studies reported statistically significant improvements in various PD parameters, the absolute changes may not be appreciated clinically.

Combination therapy of PRP and HA

Virag and colleagues investigated the effect of a combination of PRP and HA for the treatment of PD (9). In their study, patients were injected with 8 mL of PRP and HA directly into the tunica albuginea and repeated 4 times over 2 months (n=90). They noted improvements across several Peyronie's Disease Questionnaires (PDQ): PDQ1, 0.720–2.968, $P=0.002$; PDQ2, 0.275–3.225, $P=0.021$; PDQ3, 1.520–3.220, $P<0.001$ (9). Patients with prior ED (n=11) were found to have decreased in their deformation, improvement in erections, easier sexual activity, and improvement in their first condition. The mean reduction of angulation was 18.08° at 2 months, and 73.3% of these ED patients proved satisfactory results (9). However, this study lacked a control group, making it difficult to gain meaningful insight into this combination therapy compared

to the current standard of care.

ESWT

ESWT was initially explored as an alternative to invasive surgical options. Proposed mechanisms of action included a breakdown of fibrotic tissue by shockwaves and induction of inflammatory response for plaque lysis and removal (10). Claro *et al.* examined the role of ESWT and high dose vitamin E compared to vitamin E alone (11). Of 25 men treated with the dual therapy, 18 (72%) reported a decrease in curvature with a mean reduction of 21° at 3 months. Similarly, Di Mauro *et al.* observed in 325 men treated with shockwave therapy that penile plaque size improved from 1.78 to 1.53 cm^2 , penile length increased from 13.0 to 14.0 cm, pain on VAS decreased from 7 to 3, as well as improvement in each IIEF sub-domain ($P<0.001$) and all three PD questionnaire domains ($P<0.001$) (12).

The study by Claro *et al.* is limited by small sample size and lacks long-term follow-up (11). The lack of randomization in both the 2004 study by Claro and the 2019 study by Di Mauro make the studies prone to selection bias (11,12). Also, the open-label design without control for both studies may affect clinical outcomes.

SCT

SCT is an emerging modality of treatment for PD. Although the exact mechanism of action is unknown, proposed theories include upregulation of cytokines and trophic factors, reduction in inflammation and oxidative stress, extracellular matrix modulation, and differentiation into target cells to replace damaged tissue (13). Recently, mesenchymal stem cells have gained popularity over embryonic stem cells due to the ethical and logistical challenges associated with the latter. Mesenchymal stem cells are pluripotent and easily accessible, originating from a variety of tissues, including fetal tissue, umbilical cord blood, and adult tissues. Studies have examined the treatment of ED with adipose-derived stem-cells (ADSC). In animal models of ED from vascular or neurological deficits, ADSC has been shown to improve penile hemodynamics (14–16).

Using human ADSC on TGF- β treated rat models (n=27), Castiglione *et al.* reported decreased expression of disordered collagen type III and elastin, which are found in PD plaques, by 69.9% and 47.7%, respectively (17). In addition, they found a statistically significant improvement

in erectile function (intracavernous pressure/mean arterial pressure 0.37 untreated *vs.* 0.59 treated, $P=0.03$) Gokce and colleagues reported downregulation of tissue inhibitors of metalloproteinases (TIMPs) and increased expression and activity of matrix metalloproteinases (MMPs) with rat ADSC injections with or without interferon α -2b in TGF- β treated rats ($n=24$ and $n=36$) (18,19). This attenuates the fibrotic response and increases collagen degradation. ADSC has also been studied in tunica albuginea reconstruction in rat models. Ma *et al.* reported that ADSC-seeded grafts resulted in better preserved cavernosal tissue ($P<0.001$) and erectile function ($P<0.05$) than graft alone in rats undergoing bilateral incision of tunica albuginea (20).

In human trials, Levy *et al.* treated 5 patients with a total of 10 Peyronie's plaques with a single injection of placental matrix-derived mesenchymal stem cells (PM-MSC) derived from chorionic placenta (21). Plaque volumes were reduced by 33.3–98.7% at 6 weeks, 45.8–100% at 3 months, and close to 100% at 6 months. Mean reduction in curvature at 6 weeks was 49.7°. Overall, the study noted an improvement in curvature ranging from 30–120°. Peak systolic velocity also improved. There were no statistically significant differences in stretched penile length (15.2 cm baseline *vs.* 15.5 cm at 3 months).

While autologous SCT in PD is exciting due to its pluripotency and minimal risk of rejection, this treatment is still in early experimental phases. At present, most studies are based on rat models with TGF- β induced PD (17–21). Given the limitations of animal models, most studies focus on ED, histopathological, and biochemical changes. To date, there is only one study involving humans ($n=5$) (20). Furthermore, the use of stem cells in regenerative therapy is still controversial due to its oncogenic potential and long-term safety. There are currently no studies comparing oncogenicity between intact and lysed ADSC.

MMF

While primarily used as an immunosuppressant in organ transplantation, mycophenolate mofetil (MMF) has previously been shown to reduce collagen synthesis and fibroblast activity with some success in treating retroperitoneal fibrosis (22). Earlier this year, Antoniassi and colleagues reported the use of MMF on rat models with TGF- β induced PD ($n=20$) (23). Histochemical and stereological analyses demonstrated that the architecture of elastin and relative proportions of collagen types III and I approached normality following thirty days of MMF (Type

III/Type I ratio: control 0.42, TGF- β 0.82, MMF-7 days 0.65, MMF-30 days 0.31). This suggests that MMF may be a practical anti-fibrotic agent in PD. However, this study is limited by the small sample size, use of animal models, and the lack of durable long-term data. The authors also note that future studies should determine therapeutic doses for PD.

H-100

Most therapies described thus far target stable Peyronie's plaques as opposed to acute phase disease. H-100 is a novel topical agent aimed to address this space. It consists of nifedipine as an anti-fibrotic agent like verapamil, superoxide dismutase as an anti-inflammatory by targeting free oxygen radicals, and emu oil as a transdermal carrier agent. Twidwell and Levine studied H-100 in a prospective randomized trial of patients with acute phase PD (<12 months duration, $n=22$) (24). Following six months of therapy, improvements were noted in mean stretched flaccid penile length (22.6%, mean =2.4 cm, range =0.7–4.3 cm, $P=0.0002$), mean curvature (40.8%, mean =20.2 degrees, range =3–55 degrees, $P=0.001$), and mean pain level (85.7%, mean =3.0, range =0–8, $P=0.004$). Similar benefits were observed in the crossover patients from the placebo group. This topical treatment was well tolerated with only a mild rash reported in three of the 22 patients. While this pilot study demonstrates the safety of H-100, larger trials are needed to determine its efficacy and histochemical analyses can be used to examine the connective tissue changes and extent of H-100 penetration into the tunica albuginea (24).

Discussion

At this time, the evidence supporting non-conventional treatments for PD is limited. Although PRP, HA, combination therapy of PRP and HA, ESWT, SCT, MMF, and H-100 are currently offered in some clinical settings, the quality of evidence is poor due to the methodological limitations highlighted above.

There are currently no recommended oral therapies for the correction of PD according to the Canadian Urological Association (CUA), American Urological Association (AUA), and European Association of Urology (EAU) guidelines (Table 2) (25–27). For pain management during the active form of the disease, nonsteroidal anti-inflammatory drugs (NSAIDs) are recommended, along with limiting positions during intercourse to minimize

Table 2 Current recommendations for non-conventional therapies for Peyronie's disease

Treatment	Canadian Urological Association (CUA, 2018)	American Urological Association (AUA, 2015)	European Association of Urology (EAU, 2017)
Platelet-rich plasma (PRP)	No Level 1–4 or Grade A-C Evidence for treatment of PD. All current commercial and FDA therapies are not recommended as treatments for PD	Not available	Not available
Hyaluronic acid (HA)	Not recommended to use HA therapies for the treatment of PD	Not available	Not available
Extracorporeal shockwave therapy (ESWT)	Level 2 evidence, Grade C recommendation. Does not support the use of ESWT for reduction of penile curvature or plaque size	Not recommended to use ESWT for reduction of penile curvature or plaque size in PD (moderate recommendation; evidence strength Grade B). Clinicians may offer ESWT to improve penile pain (conditional recommendation; evidence strength Grade B)	ESWT fails to improve penile curvature and plaque size but may be beneficial for penile pain in PD (Level 1C evidence, Grade B recommendation)
Combination hyaluronic acid and platelet rich plasma	Not available	Not available	Not available
Stem cell therapy (SCT)	Not recommended as a treatment for PD	Not available	Not available
Mycophenolate mofetil (MMF)	Not available	Not available	Not available
H-100	Not available	Not available	Not available

pain during penetration (25–27). Oral phosphodiesterase-5 (PDE-5) inhibitors are used in patients to improve ED associated with PD (25).

For the correctional treatment of PD, intralesional therapies are recommended. These include the administration of Collagenase Clostridium Histolyticum (Xiaflex®), interferon α -2 β , or verapamil (25–28). Collagenase Clostridium Histolyticum is the first FDA, and Health Canada approved therapy for PD (28). The CUA and AUA recommend that clostridial collagenase should be used as first line, followed by verapamil or interferon α -2 β as the second line (25,26). In terms of mechanical therapy, penile traction or vacuum pump are recommended as they are shown to correct penile pain and support penile length (25–27). Surgical treatments include penile plication, plaque excision/incision, and grafting, or implantation of a penile prosthesis.

At present, there are several limitations preventing broader applicability of the presented non-conventional PD therapies. Firstly, many of the proposed treatments are still in experimental stages and lack robust randomized control trials in patient populations. Secondly, head-to-head

studies comparing these treatments to the standard of care are lacking and would be important for stakeholders when updating clinical guidelines. Thirdly, reporting of statistically significant improvements in PD parameters must also be clinically relevant. Lastly, current studies offer limited discussion on complication rates, cost, and availability, which is essential for patients and providers when making informed decisions about treatment. While the prospect of integrating these treatments into gamut of validated PD therapies is enticing, the current evidence supporting these options is limited and still leaves much to be desired. Until more higher-level evidence is available, patients should be cautioned against using these non-conventional treatments in place of the accepted standard of care.

One must consider why such an explosion of novel therapies exists. From a patient perspective, there is an enormous demand for safer, more effective, and cheaper options. Providers and academics may be motivated by financial and research incentives. As we continue to find new targets for therapies, we may gain added insight into the pathogenesis of PD. Finally, pharmaceutical companies may be interested in entering this market and are facilitated

by the availability of direct-to-consumer advertising.

Conclusions

While there are several non-conventional therapies for PD available, the limited and low quality of evidence supporting these alternatives precludes their use as the standard of care. Physicians play a significant role in providing evidence-based recommendations and addressing patient concerns regarding these non-conventional therapies. At this time, larger, randomized prospective studies are needed to understand the therapeutic value better and the risks of these alternatives.

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Footnote

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