Expert Opinion on Pharmacotherapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieop20

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To cite this article: Eric Chung & Faysal A. Yafi (2022): Pharmacotherapy in Peyronie's disease: a state-of-the-art review on established contemporary and emerging drugs, Expert Opinion on Pharmacotherapy, DOI: 10.1080/14656566.2022.2043274

To link to this article: https://doi.org/10.1080/14656566.2022.2043274

Published online: 25 Feb 2022.

EXPERT OPINION ON PHARMACOTHERAPY
https://doi.org/10.1080/14656566.2022.2043274

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REVIEW

Pharmacotherapy in Peyronie's disease: a state-of-the-art review on established contemporary and emerging drugs

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ABSTRACT

Introduction: Current clinical guidelines on Peyronie's disease (PD) advocate non-surgical treatment options as the first-line therapy despite inconsistent clinical outcomes when compared to definitive penile reconstructive surgery.

Areas covered: This article examines the current understanding of established contemporary and emerging pharmacotherapies for PD. Emphasis has been placed on published clinical studies on drugs in the last 10 years.

Expert opinion: Published studies have shown that combination therapy is likely more effective than monotherapy. Combined treatment modalities involving various oral and/or intralesional pharmacotherapies together with mechanical devices or clinical psychosexual therapy may provide additional or synergistic benefits for PD patients. A multidisciplinary approach coupled with more novel targets for pharmacological intervention could deliver a more effective treatment paradigm to prevent or at least delay the need for definitive penile reconstructive surgery. Drugs targeting the inhibition of TGF-β1 pathway and myofibroblast transformation are of great interest and studies into next-generation genetic sequencing and transcriptional biomarker regulatory pathways in PD will provide useful insights into the pathophysiology of PD, and assist the development of future regenerative technology including cellular-based therapies to target various anti-fibrotic molecular mechanisms and the potential to be integrated into existing treatment armamentarium for PD.

ARTICLE HISTORY
Received 12 November 2021
Accepted 14 February 2022

KEYWORDS
Peyronie's disease; drug therapy; intralesional injections; penile induration; treatment outcome

1. Introduction

Peyronie's disease (PD) is often defined by the presence of penile plaque(s) and various penile complaints such as penile pain, curvature, and/or deformity [1–4]. While the basic pathophysiology is thought to arise from abnormal penile healing secondary to repetitive injury with ensuing extravasation and accumulation of various pro-fibrotic factors (especially transforming growth factor beta-1, TGFβ1), fibrin, and myofibroblast between the tunica layers following injury, the development of PD is more common in genetically susceptible individuals and in certain high-risk populations such as diabetic males or those with fibrotic disorders or post-prostate cancer treatment [5,6].

Current clinical guidelines on PD advocate non-surgical treatment options as the first-line therapy unless patients wish to undergo penile reconstructive surgery for the definitive solution and are willing to accept surgical risks [7,8]. Epidemiological studies have shown natural resolution is uncommon without intervention (12%) [9]. While the success rate of medical therapy for PD can be inconsistent when compared to penile reconstructive surgery, it is often prescribed in the early stage of PD to resolve or stabilize penile curvature, pain, and plaque size. However, most drugs to treat PD are used off label apart from collagenase *Clostridium histolyticum*. The following article examines the current state-of-the-art understanding of established contemporary and emerging pharmacotherapies for PD.

2. Methods and materials

A Medline search on relevant English-only articles on PD was undertaken using the following search key terms: "Peyronie's disease," "oral drug," and "intralesional injection." A detailed analysis of all drug therapies on PD is not intended in this narrative review and the emphasis is placed on published clinical studies on both oral and intralesional drugs in the last 10 years. Novel drugs currently in the development pipeline for PD will be reviewed too. Given the poor outcomes of the topical drugs for iontophoresis therapy in PD, the focus of this paper will focus on oral and intralesional drugs only. The discussion on the mechanism(s) of action for each drug will be covered (Table 1) and a contemporary perspective on PD treatment strategies for PD will be included in the Expert Commentary section.

3. Oral and intralesional drugs for PD

3.1. Potaba

Potassium para-aminobenzoate or otherwise known as Potaba has been used in PD since the 1980s. Potaba has an anti-

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inflammatory property that results in the inhibition of abnormal fibroblast proliferation and secretion of acid mucopolysaccharide and glycosaminoglycan [10]. While older published placebo-controlled randomized controlled studies on Potaba have reported mixed clinical outcomes in terms of delaying the progression and decreasing penile pain, its positive impact on penile curvature is limited [11,12]. More recently, Potaba monotherapy was shown to equally improve penile pain and plaque size as well as penile curvature when compared to combination therapy (tamoxifen, L-carnitine, and tadalafil), although the dropout rate was significantly higher in the Potaba group (68.2% vs 7.7%) [13]. While this study failed to show any statistically significant difference between the two treatment arms owing to the high dropout rate, combination therapy demonstrated a better response rate in patients whose penile curvature angle was less than 30° (44.4% vs. 79.1%, $p = 0.048$) and a higher rate of successful sexual intercourse (42.8% vs. 78.3%, $p = 0.034$).

3.2. Estrogen receptor modulators

Tamoxifen is a non-steroidal anti-estrogen that possesses antifibrotic effects through the inhibition of TGFβ1 secretion from fibroblasts via the non-SMAD pathway [14,15]. While tamoxifen has been effective in treating other fibrotic disorders such as retroperitoneal fibrosis [16], its efficacy in patients with PD has been inconsistent especially in an earlier publication [17]. However, a recent study indicated that combining tamoxifen and phosphodiesterase type 5 inhibitors (PDE5i) might be effective in treating PD based on in vitro and in vivo disease models through synergistic effects by inhibiting myofibroblast transformation, collagen gel contraction, and extracellular matrix production [18]. The same group published an updated study [19] that showed tamoxifen prevents myofibroblast transformation until 36 hours after TGF-β1 treatment, whereas vardenafil could prevent only 24 hours after TGF-β1 treatment, with downregulation of phosphodiesterase 5A and estrogen receptor (ER)-β as well as antifibrotic signaling pathways, peroxisome proliferator-activated receptor gamma and beta glycan (TGFB receptor III).

The role of adenosine receptors (ADOR) A1 and A2B in myofibroblast transformation in PD has been investigated recently and BAY 60–6583, an ADOR A2B agonist was found to significantly inhibit the myofibroblast transformation in response to TGF-β1 [20]. Similarly, Rho-kinase (ROCK) inhibitor has been shown to attenuate TGF-β1 signaling and myofibroblast transformation [21]. Y-27632, a ROCK inhibitor, coupled with simvastatin has also been shown to suppress the TGF-β1-induced myofibroblast transformation in the PD model by preventing nuclear translocation of YAP/TAZ proteins [22]. While fasudil is the only available ROCK-inhibitor currently in clinical use for angina and cerebral vasospasm [23], it remains to be determined whether the observed beneficial effects of this drug can be safely trialed in PD men without incurring serious side effects.

3.3. Colchicine

Colchicine is an alkaloid that inhibits the microtubular structure and function which is critical in the anti-inflammatory activity [24]. Earlier studies reported that colchicine has mixed effects in terms of reducing penile pain, curvature and plaque size [25–27]. A recent study reported that intralesional injection of thiocolchicine, a semi-synthetic colchicine derivate [28] appeared to be more effective than verapamil in reducing penile curvature (69% vs 66%), and plaque size (61% vs 7%) while improving sexual function.

3.4. Phosphodiesterase inhibitors

Pentoxifylline is a nonspecific phosphodiesterase inhibitor (PDEi) and a methylxanthine derivative that has been used to treat peripheral vascular diseases due to its antiplatelet and antioxidant properties [29]. Furthermore, it has been

Table 1. Published studies on drug therapies for Peyronie's disease (in the last 10 years).

Drugs	Proposed mechanisms of action	Published studies (Reference)	Comments
Potaba	Inhibits abnormal fibroblast proliferation and secretion of acid mucopolysaccharide and glycosaminoglycan	13	Higher drop-out rate, and potentially less effective compared to combination therapy
Estrogen receptor modulators	Anti-fibrotic effects through the inhibition of TGFβ1 secretion from fibroblasts via the non-SMAD pathway	18,19	Potential synergistic effect combining tamoxifen and PDE5i
Colchicine	Inhibits microtubular structure and function	28	Intralesional injection of thiocolchicine appeared more effective than verapamil
PDEi/PDE5i	Decreases various pro-inflammatory cytokines and attenuates the TGF-β1 associated fibrotic process	34–39, 41–45	Combination therapy is effective in reducing plaque volume and curvature and improving erectile function
Collagenase *Clostridium histolyticum*	AUX-I and AUX-II isoforms; degrades collagen type 1 and III	49–70	Expansion on original criteria on IMPRESS trials and penile modeling is necessary
Hyaluronic acid	Anti-inflammatory and immunosuppressive properties	77–79	Can be used as combined oral and intralesional therapy
Verapamil	Interfere with fibroblast proliferation and modulate collagen biosynthesis	88	Combined therapy appears more effective
Interferon alpha-2B	Immune modulator	94–97	Combined therapy appears more effective
Regenerative therapy	Immune modulator and effects on metalloproteinases and myofibroblast activity	106–108, 111	Data not available yet
Botulinum toxin	Unknown- disruption or relaxation of plaque	113	A single pilot study shows a promising outcome

(PDEi = phosphodiesterase inhibitor; TGFβ1 = transforming growth factor; IMPRESS = Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies)

shown that pentoxifylline can reduce various proinflammatory cytokines and attenuate the TGF-β1 associated fibrotic process [30,31]. Published literature reported that pentoxifylline can be effective at improving penile curvature and erectile function while reducing plaque size [32,33]. Furthermore, the biopsy of samples of tunica albuginea-derived fibroblasts treated with pentoxifylline showed a reduction in TGF-β1-mediated increase in elastogenesis and collagen deposition. The role of combination therapy using pentoxifylline, L-arginine, and verapamil injections demonstrated a significant penile curvature improvement despite the use of penile traction therapy [34] while combined pentoxifylline and intralesional verapamil were more effective than pentoxifylline monotherapy or intralesional verapamil alone with regard to improvements in penile curvature (36.7% vs 26.7% vs 36.7%), ED (86.7% vs 46.7% vs 66.7%) and penile pain (80% vs 73.3% vs 76.7%) [35]. Co-administration of oral and penile injection of pentoxifylline together with other oral antioxidant and anti-inflammatory agents have been found to decrease plaque volume, calcification size, penile pain, and curvature [36]. A recent study with pentoxifylline and/or colchicine together with penile traction therapy improved penile curvature and reduced plaque size but there was no statistically significant difference between the colchicine or pentoxifylline arm [37].

Specific PDE5i drugs such as tadalafil daily therapy have been shown to reduce plaque volume and improve erectile function when used in conjunction with pentoxifylline [38,39]. PDE5i is thought to remodel penile fibrosis by decreasing the degradation of cGMP and therefore increasing NO downstream signaling [31]. Published studies over the past decade have shown that tadalafil can be effective either as monotherapy [40,41] or in combined therapy with shockwave therapy [42] or intralesional injections [43,44].

3.5. Collagenase clostridium histolyticum

Collagenase *Clostridium histolyticum* (CCH) was first studied in PD in the early 1980s [45,46] and to date, remains the only drug approved specifically for PD [47]. The commercially marketed CCH consists of two isoforms of synergistically acting collagenases, AUX-I and AUX-II which are responsible for the degradation of collagen type I and III, the main contributors to PD plaque formation [47]. Furthermore, studies have shown that CCH directly induces apoptosis of fibroblasts, downregulates the abnormal expression of collagen type I and III, and destroys pathological collagen plaques [47]. In the original IMPRESS (Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) clinical trials, patients received up to 3–4 cycles of two injections of CCH at the point of maximum curvature of the plaque, given between 24 to 72 hours followed by strict instruction on manual penile remodeling [46,47]. Since then, more than 100 studies have been published showing intralesional CCH therapy to improve penile curvature (and erectile function) while reducing plaque volume [48–51].

Patients with pre-treatment penile curvature between 30 and 60 degrees, mild-to-moderate baseline sexual function, stable disease (at least 6 months) and low calcification within plaques are favorable candidates for CCH therapy [52,53]. There are numerous clinical studies, especially single-arm clinical trials assessing various modifications to treatment protocols that indicate dosing adjustments [54–59] and intralesional injection techniques [60,61] can be made to shorten treatment duration and potentially reduce procedural morbidity without compromising on the clinical outcomes. Furthermore, some studies have expanded the inclusion criteria for CCH therapy to include males with ventral curvature [62] and atypical deformity [63–65]. The role of combination CCH injections with other treatment modalities showed a greater improvement in penile curvature than monotherapy, although further studies are required to determine whether combination therapy provides additive or synergistic benefits [66–71]. The most recent update on CCH is its untimely withdrawal from commercial markets in European and Australasian countries [47,72], and the cost for CCH remains significant in non-funded healthcare systems.

3.6. Hyaluronic acid

Hyaluronic acid, the main component of the extracellular matrix, possesses both anti-inflammatory and immunosuppressive properties critical to tissue regeneration [73–75]. Recent published multicenter randomized controlled trial found intralesional hyaluronic acid to have greater improvements in penile curvature and patient satisfaction rate than verapamil injections [76]. Furthermore, a prospective clinical study with a similar trial design demonstrated that intralesional hyaluronic acid was an effective and reliable treatment option to manage males with PD in the acute phase [77]. Combined oral and intralesional hyaluronic acid therapies provided a greater efficacy in the improvements of penile curvature and overall sexual satisfaction than intralesional hyaluronic acid monotherapy [78].

3.7. Verapamil

Verapamil is a calcium channel blocker that has been shown to interfere with fibroblast proliferation and modulate collagen biosynthesis by decreasing collagen deposition and upgrading collagenase activity [79,80]. While prior open-labeled studies have shown intralesional verapamil therapy to be effective in PD [35,81–83], the limited randomized placebo-controlled trials reported mixed outcomes in curvature, plaque size, or penile pain reduction when compared to placebo [84,85]. Comparing combination therapy with intralesional verapamil, oral pentoxifylline, and L-arginine (group 1) against the same medical therapy and adjunctive penile traction therapy (group 2), there was a trend toward less penile curvature with a significant gain in stretched penile length following a longer duration of use of the traction device (0.38 cm gain for every hour per day of traction therapy on the multivariate analysis) [34].

3.8. Interferon alpha 2B

Interferon is a low molecular weight protein that can induce immune modulation through various antiproliferative effects and interferon alpha-2B balances the expression of pro- and anti-inflammatory agents [86]. From the early pilot study [86] to subsequent larger studies from the same group [87–89] to the randomized placebo-controlled trial [90], intralesional interferon alpha-2B injections resulted in statistically significant improvements in penile curvature, plaque size and density, and pain on erection. More recent updates on interferon alpha-2B have demonstrated the improvement in penile curvature was independent of the pretreatment curvature or duration of PD [91,92].

The role of combination interferon alpha-2B with penile traction therapy demonstrated a slight marginal improvement in penile curvature compared to interferon monotherapy [93]. More recently, another group found that interferon alpha-2B and verapamil had almost similar clinical outcomes in terms of improvement in penile curvature, plaque volume, and pain on erection, but verapamil had a lower cost [94]

3.9. Regenerative therapy: stem cells and platelet-rich plasma

Although stem cell is not technically a drug, its administration is like intralesional injection therapy. In recent years, cellular-based technology with stem cell's therapy (SCT) has been utilized to treat PD [95,96]. While the exact mechanism of action for SCT in PD remains largely unknown, it is thought that intralesional injection of stem cells would have an immunomodulatory effect through its anti-inflammatory and anti-fibrotic actions as well as decrease the expression of tissue inhibitors of metalloproteinases and enhance the expression of matrix metalloproteinases, thereby reducing Peyronie's plaque.

Moreover, it has been demonstrated that intralesional allogeneic adipose-derived stem cells could decrease the expression of tissue inhibitors of metalloproteinases and enhance the expression of matrix metalloproteinases [97] while inhibiting the Rho/RhoA and SMAD signaling pathways responsible for myofibroblast activity [98]. While several basic science studies on intralesional SCT in animal models of PD have shown encouraging outcomes [99–102], its translation to a clinical trial is difficult and very limited with suboptimal clinical outcomes. Furthermore, the effects of different types of SCT in plaque remodeling and longer-term clinical efficacy, durability, and safety need further study. To date, the only known human trial of SCT in PD utilized penile injection of placental matrix-derived mesenchymal stem cells (PMD-MSC) has been published and 7 out of 10 plaques injected with PMD-MSC disappeared completely at 3-month review although there were no significant improvements in penile size or blood flow [103]. Other registered clinical trials on SCT include cultured allogeneic adult umbilical cord stem cells [104] and autologous stromal vascular fraction [105].

In recent years, there has been considerable interest in the role of platelet-rich plasma (PRP) as an alternative to SCT due to easier preparation and a reasonable safety profile [106]. While there have been several animal studies of PRP in PD [107], so far only one randomized, double-blind, placebo-controlled, crossover human trial on the efficacy and safety of platelet-rich plasma has been registered with an estimated study completion date in mid-2023 [108].

3.10. Botulinum toxin (Botox)

There has been considerable interest in expanding the use of botulinum toxin to treat sexual medicine conditions although the exact mechanism(s) of action in PD remains largely unknown [109]. The role of intralesional Botox injection has been investigated in a randomized, placebo-controlled, crossover single-center trial. In this pilot study, there was a 21.7% improvement in penile curvature found in the patients who received 100 units of Botox injection [110].

4. Expert opinion

PD is an abnormal connective tissue disorder and is often characterized by the presence of (inflammatory) plaque within the bilaminar tunica albuginea [5] secondary to aberrant wound healing and erroneous genetic neurohumoral pathways [1,3]. Hence, the prescribed drug therapy will need to remodel the existing Peyronie's plaque and address the underlying fibrotic process. Current clinical guidelines advocate the use of an oral drug as first-line treatment despite the relative sparse scientific evidence and the fact that published studies have significant heterogeneity in methodologies such as a small number of patients, mixed PD features, and limited objective outcome measures. The suboptimal efficacy of oral drug therapy relates to the lack of localized drug absorption and penetration to achieve sufficient drug concentration within the penile plaque. As expected, transdermal application of drugs with or without iontophoresis therapy is likely to be ineffective, and published guidelines do not recommend topical therapy in PD. Despite the relative paucity of high-quality evidence with the use of oral monotherapy, oral drugs may be useful in the early phase of PD with unstable or progressive penile curvature when the (inflammatory) plaque is not fully formed yet. Furthermore, for males who are not interested in surgical intervention, oral drugs can be used as an adjunct with other non-surgical therapy. Recent studies highlight a potential positive role of oral agents such as tamoxifen, pentoxifylline, and PDE5i in PD.

While intralesional drugs appear more effective than oral drugs since they are injected directly into the Peyronie's plaque, published clinical outcomes are mixed and this reflects the heterogeneous nature of PD with various presentations of atypical disease, at times the absence of a palpable plaque for injection, level of clinical experience in delivering intralesional therapy and optimal intralesional treatment protocols [53]. Placebo-controlled trials showed that injection of saline and the amount volume of injection can improve penile curvature and plaque size [1,4]. Furthermore, penile remodeling was not commonly administered at the time of intralesional therapy before the publication of the IMPRESS trials [48] and the lack of manual

remodeling may play a factor in the suboptimal outcomes observed with other intralesional drugs therapy. To date, CCH remains the only licensed drug in PD. Nonetheless, CCH is an expensive, likely not cost-effective therapy when compared to definitive penile reconstructive surgery, and its availability is largely limited to the North American market only.

Published studies have shown that combination therapy is likely more effective than monotherapy. Combined treatment modality involving various oral and/or intralesional pharmacotherapies together with mechanical devices or clinical psychosexual therapy may provide additional or synergistic benefits for PD patients. A multidisciplinary approach coupled with more novel targets for pharmacological intervention could deliver a more effective treatment paradigm to prevent or at least delay the need for definitive penile reconstructive surgery. Larger, multicenter clinical trials with uniform research methodology and treatment protocols, with a greater emphasis on patient-reported outcomes and cost-effectiveness analysis, as well as utilizing generated proteomic, genomic, and metabolomic data will be useful to direct future PD management.

Current in vivo PD models have highlighted that TGF-β1-mediated activation of myofibroblasts appears to be the common denominator to PD [5], and hence, drugs targeting the inhibition of the TGF-β1 pathway and myofibroblast transformation are of great interest and likely form the new frontier in PD therapy. Drugs that enhance the expression of tissue inhibitors of metalloproteinases and/or inhibit the function of matrix metalloproteinases will provide a new avenue to redress the balance between pro-fibrotic and anti-fibrotic roles. Studies into next-generation genetic sequencing and transcriptional biomarker regulatory pathways in PD will provide useful insights into the pathophysiology of PD, and assist the development of future regenerative technology including cellular-based therapies to target various anti-fibrotic molecular mechanisms and the potential to be integrated into existing treatment armamentarium for PD. Further research is needed to develop and testing of these novel pathways and this needs to be matched with greater public awareness and patient education on PD to streamline the clinical care pathway for this debilitating heterogeneous and complex psychosexual condition.

Highlight box

- Current clinical guidelines advocate the use of drug therapy as first-line treatment despite the relative sparse scientific evidence and the fact that published studies have significant heterogeneity in methodologies such as a small number of patients, mixed PD features and limited objective outcome measures.
- Oral drugs may be useful in the early phase of PD and for males who are not interested in surgical intervention, oral drugs can be used as an adjunct with other non-surgical therapy.
- Intralesional injectable drugs appear more effective than oral drugs but require injection into palpable penile plaque while the optimal intralesional treatment protocol(s) including amount of drug injection as well as penile remodeling strategy remain unknown.
- Combined treatment modality involving various oral and/or intralesional pharmacotherapies together with mechanical devices or clinical psychosexual therapy may provide additional or synergistic benefits for PD patients.
- Future drug therapy will need to incorporate drugs that target matrix metalloproteinases and tissue inhibitor of metalloproteinases as well as various genetic and molecular regulatory pathways involved in the PD.

Declaration of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

Funding

This manuscript has not been funded.

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