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Pharmacological Management of Peyronie's Disease

Landon W. Trost, *Serap Gur* and *Wayne J.G Hellstrom*

Department of Urology, Tulane Health Sciences Center, New Orleans, Louisiana, USA

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Abstract

Peyronie's disease is a localised, fibrosing condition of the penis that occurs in up to 9% of men. Although its aetiology has not been elucidated, Peyronie's disease probably results from the presence of a predisposing genetic susceptibility combined with an inciting event, most probably trauma. Following appropriate clinical evaluation, initial treatment consists of a trial of oral and/or intralesional pharmacotherapy. Oral therapies most commonly employed include para-aminobenzoate (Potaba®) and tocopherol (vitamin E), with colchicine, tamoxifen, propoleum and acetyl-L-carnitine being used less frequently. Placebo-controlled studies examining these agents have failed to show a consistent beneficial effect on Peyronie's disease, with the exception of para-aminobenzoate, which may decrease plaque size and curvature, and acetyl-L-carnitine, which may reduce erectile pain and inhibit disease progression. Intralesional injection therapy for Peyronie's disease is commonly used as a first-line therapy along with oral

medications. The current standard of care involves injection with interferon-α-2a or -2b, verapamil or collagenase over 2-week intervals for a period of 5–6 months. Interferon-α-2b, in particular, has been documented in a large, multicentre, placebo-controlled study to be significantly more effective than placebo in decreasing penile curvature, plaque size, penile pain and plaque density. However, interferon treatment is also associated with significant adverse effects, including fever and other flu-like symptoms. Other available therapies that have not consistently shown efficacy in placebo-controlled studies include corticosteroids and orgotein. Surgery is considered in patients with Peyronie's disease who have not responded to a trial of conservative medical therapy for 1 year and who are precluded from sexual intercourse. Procedures commonly performed include the Nesbit procedure (or variations of the Nesbit), penile plaque incision/excision with or without grafting, and implantation of a penile prosthesis. Further basic scientific research in Peyronie's disease is likely to identify additional targets for future pharmacotherapy.

Peyronie's disease is a localised, connective tissue disorder characterised by changes in the collagen composition that results in abnormal deposition of fibrous tissue in the tunica albuginea of the penis. Although the disorder was described as early as 1587 by Guilio Cesare Aranzi, who called it a "rare affection of the genitals in people with excessive sexual intercourse", the eponymous term for the condition arose after Francois Gigot de la Peyronie, the personal physician of King Louis XV, reported in 1743 a case series of three patients with plastic induration and curvature of the penis.

Peyronie's disease has historically been thought to be a rare, insignificant condition. The first description of the natural history of Peyronie's disease was given by Williams and Thomas,[1] in 1970, who reported that the disease was one of 'gradual resolution'. They further stated that none of the 21 patients described in the study experienced a worsening of his condition. This led them to advocate observation and reassurance as primary therapy. Their study was hindered by a small number of study subjects, inadequate follow-up, and lack of a standardised approach and evaluation of patients with Peyronie's disease. Nevertheless, the results of this study led clinicians to adopt a conservative approach of watchful waiting as standard treatment for Peyronie's disease.

In 1990, a questionnaire-based study conducted by Gelbard et al.[2] revealed that among 97 patients with Peyronie's disease, only 13% experienced a resolution of their symptoms. They further noted that 40% of respondents perceived that their disease had progressed, and 48% considered that their condition had remained unchanged at follow-up. In addition to disease progression, these authors reported that 77% of patients experienced detrimental psychological consequences as a result of their disease process. Kadioglu et al.[3] provided additional support to the idea that Peyronie's disease was a progressive condition in a retrospective review of 307 men with the disease. They reported that spontaneous resolution was a rare occurrence and that 30.2% of those not receiving any treatment experienced substantial deterioration. Additionally, 62.5% of patients found their disorder to be 'disabling', and poorer outcomes and symptoms were associated with the presence of coexisting diabetes mellitus, hypertension or lipid abnormalities. Results from these studies suggested that despite a general perception that the condition was benign, Peyronie's disease is progressive and can have significant emotional and psychological consequences in men with this condition.

Current epidemiological estimates of the prevalence of Peyronie's disease range from 3.2%, as described in a 2001 questionnaire study involving

4432 respondents from Cologne, Germany,[4] to 8.9%, as reported in a 2004 study of 534 men who presented to American urologists for routine prostate screening.[5] Disease onset is commonly associated with preceding trauma and most often occurs in older men, although Mulhall et al.[6] have documented that the majority of men with Peyronie's disease in their series had no specific recollection of trauma, and 10% of patients experienced symptom onset before 40 years of age.

To evaluate currently employed pharmacotherapy in Peyronie's disease, a literature review was performed using MEDLINE via PubMed to retrieve articles containing the following keywords: 'Peyronie's disease', 'vitamin E', 'Potaba', 'para-aminobenzoate', 'colchicine', 'tamoxifen', 'propoleum', 'acetyl-L-carnitine', 'corticosteroids', 'orgotein', 'collagenase', 'verapamil' 'interferon', 'transdermal', 'iontophoresis', 'natural history', 'prevalence', 'risk factors', 'surgery', 'treatment' and 'pharmacotherapy'. Articles were chosen according to their relevance to the current topic, scientific merit and quality of design. When available, double-blinded, placebo-controlled studies were reviewed and compared with the current body of literature.

1. Pathophysiology

Despite being recognised by the medical community for >250 years, there has been meagre advancement by the scientific community towards understanding the underlying aetiology of Peyronie's disease and providing effective modalities for preventing and curing the condition. Peyronie's disease is commonly perceived to be a disorder of inappropriate wound healing, with its development probably resulting from both an underlying genetic predisposition in addition to the presence of an inciting event.[7] Micro-trauma has been hypothesised to contribute to the initiation of Peyronie's disease, although studies examining the incidence of Peyronie's disease following penile trauma have failed to implicate trauma as an independent, causative factor.[8,9]

Evidence for an underlying genetic predisposition towards Peyronie's disease can be found in its association with other collagen diseases such as Dupuytren's disease. One study comparing the gene expression profiles of patients with Peyronie's disease and Dupuytren's disease found similar alterations in genes responsible for collagen degradation, ossification and myofibroblast differentiation.[10] Similarly, when comparing the gene expression of Peyronie's disease plaques to normal tunica albuginea, a University of California, Los Angeles research team found that genes involved in collagen synthesis, myofibroblast differentiation, tissue remodelling, inflammation, ossification and proteolysis were upregulated, whereas genes inhibiting these processes, as well as those coding for collagenases, were all downregulated.[11] Results from both of these studies imply that patients with Peyronie's disease have an increased collagen synthesis to breakdown ratio. In the presence of a predisposition towards collagen overproduction, trauma (both minor and major) is the most likely initiating step in the pathway to this pathological process of plaque formation.[7] Other postulated factors that may play a role in the pathogenesis of Peyronie's disease include transforming growth factor-β (TGFβ), excess fibrin deposition, matrix metalloproteinase dysfunction and plasminogen activator inhibitor-1 abnormalities.[12-14]

2. Clinical Evaluation

No standard clinical assessment of Peyronie's disease has been established to date. Patients presenting with Peyronie's disease typically exhibit any single presentation or combination of penile plaque, curvature, penile pain and erectile dysfunction. Plaques are typically located on the dorsal or lateral aspect of the penis, causing an upward or lateral deflection during erection. As many patients are embarrassed by or unaware of the presence of Peyronie's disease, they are unlikely to mention the topic unless specifically questioned about it by a treating physician. In an analysis of this subject, Levine and Greenfield[15] recommended several

Table I. International Index of Erectile Function questionnaire for the quantitative evaluation of erectile dysfunction (reproduced from Rosen et al.,[16] with permission from Elsevier)

Over the past 4 weeks:
1. How often were you able to have an erection during sexual activity? 0 = no sexual activity; 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration? 0 = no sexual activity; 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
3. When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner? 0 = did not attempt intercourse; 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
4. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner? 0 = did not attempt intercourse; 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
5. During sexual intercourse, how difficult was it to maintain your erection to complete intercourse? 0 = did not attempt intercourse; 1 = extremely difficult; 2 = very difficult; 3 = difficult; 4 = slightly difficult; 5 = not difficult
6. How many times did you attempt sexual intercourse? 0 = no attempts; 1 = one to two attempts; 2 = three to four attempts; 3 = five to six attempts; 4 = seven to ten attempts; 5 = more than eleven attempts
7. When you attempted sexual intercourse, how often was it satisfactory for you? 0 = did not attempt intercourse; 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
8. How much did you enjoy sexual intercourse? 0 = no intercourse; 1 = no enjoyment; 2 = not very enjoyable; 3 = fairly enjoyable; 4 = highly enjoyable; 5 = very highly enjoyable
9. When you had sexual stimulation or intercourse, how often did you ejaculate? 0 = did not attempt intercourse; 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
10. When you had sexual stimulation or intercourse, how often did you have the feeling of orgasm or climax? 0 = did not attempt intercourse; 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
11. How often did you feel sexual desire? 1 = almost never/never; 2 = a few times (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time); 5 = almost always/always
12. How would you rate your level of sexual desire? 1 = very low/none at all; 2 = low; 3 = moderate; 4 = high; 5 = very high
13. How satisfied were you with your overall sex life? 1 = very dissatisfied; 2 = moderately dissatisfied; 3 = about equally satisfied and dissatisfied; 4 = moderately satisfied; 5 = very satisfied
14. How satisfied were you with the sexual relationship with your partner? 1 = very dissatisfied; 2 = moderately dissatisfied; 3 = about equally satisfied and dissatisfied; 4 = moderately satisfied; 5 = very satisfied
15. How do you rate your confidence that you could have and keep an erection? 1 = very low; 2 = low; 3 = moderate; 4 = high; 5 = very high

components that should be included in an initial evaluation, and which are reviewed briefly here.

All assessments of Peyronie's disease should begin with a thorough history, gathering information about disease onset and duration, the presence of precipitating trauma, the degree of penile deformity, curvature and erectile rigidity/dysfunction, and the subjective level of sexual ability. It is also important to understand the degree of emotional and psychological impact that this disease has had on the patient's interpersonal relationships, as this may encourage a more thoughtful and possibly aggressive treatment approach. A more detailed medical and sexual history can often be rapidly obtained through the use of standardised questionnaires, such as the International Index of Erectile Function (IIEF) [table I] and the Peyronie's Disease Index (PDI).[15] These may also serve as means for objective follow-up to measure treatment efficacy over time. Information obtained about a patient's medical history

should focus on risk factors associated with erectile dysfunction, such as hypertension, hyperlipidaemia, diabetes or the presence of coronary artery disease.

Physical examination begins with a standard genitourinary evaluation and includes observation for the presence of Dupuytren's contracture or Ledderhose scarring (plantar fibromatosis), both of which are associated with an increased incidence of Peyronie's disease. Objective measurements include documentation of the stretched penile length, plaque characteristics, location and size, and the presence or absence of tenderness to palpation.

Laboratory studies do not serve an essential role in the diagnosis or management of Peyronie's disease, but may include serum testosterone, glucose, prostate-specific antigen and a lipid panel according to the clinical presentation (i.e. erectile dysfunction). Objective imaging may be obtained via penile duplex Doppler ultrasonography (PDDU) to record penile vascular flow, venous leakage and erectile response, as well as plaque size, location and the presence of calcifications. Penile curvature is measured using a standard instrument, such as a protractor. These measurements provide a standard against which progression or regression of the disease can be measured at future visits.

Taking into account the natural history of Peyronie's disease and the results of appropriate clinical evaluation, considerations for appropriate therapy can be made on the basis of the patient's erectile status, presence of bothersome symptoms such as pain, patient motivation for treatment, and the overall psychological status. In most patients, the standard of care involves an initial trial of either oral or intralesional therapies during the first 6–12 months of treatment.[17] Commonly prescribed oral therapies include tocopherol (vitamin E) and para-aminobenzoate (Potaba®)[1], with colchicine, tamoxifen, propoleum and acetyl-L-carnitine used less frequently. Intralesional therapy involves repeated injections of verapamil, interferon-α-2a or -2b or collagenase directly into the penile plaque over 2-week intervals (bi-weekly) for at least 6 months. Other available intralesional therapies include corticosteroids and orgotein, which have not shown any efficacy to date. Table II highlights proposed mechanisms of action for the above-listed therapies in Peyronie's disease as well as reported adverse effects. Each of these therapies is discussed in greater detail in sections 3 and 4.

3. Oral Pharmacotherapy

3.1 Tocopherol (Vitamin E)

Tocopherol is a fat-soluble compound that functions as a natural antioxidant to reduce the number of oxygen free radicals produced in energy metabolism. It has also been shown to play a role in DNA repair and in immune modulation.[18] The widely accepted use of tocopherol in the treatment of Peyronie's disease has been hypothesised to inhibit fibrosis by acting as a scavenger of oxygen free radicals. *In vitro* studies examining the effect of free radicals on human cavernosal cells have shown their direct association with increased collagen production.[19] It is logical to conclude that inhibition of free radicals (i.e. with use of tocopherol) should decrease the rate and degree of fibrosis. However, *in vivo* data have failed to show any benefit in patients with Peyronie's disease to date.

The first reported use of tocopherol was in a 1948 study of 23 patients that found a 91% reduction in plaque size with complete resolution of pain and a 78% decrease in penile curvature.[20] However, a double-blinded, placebo-controlled, cross-over study conducted in 1983 by Pryor and Farrell[21] failed to show similar beneficial effects for tocopherol relative to placebo. In this study of 40 patients with Peyronie's disease, an improvement in pain was noted among 35% of those receiving tocopherol, but no significant changes were observed in plaque size or penile curvature. In a more recent, retrospective analysis of 34 patients with Peyronie's disease who had received either tocopherol (for 6.1 ± 6.2 months) or no treatment, follow-up was conducted 12.6 ± 15.5 months later to evaluate for pain relief, plaque reduction or curvature change.[22] The

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table II. Summary of oral and injection pharmacotherapies for Peyronie's disease, focusing on proposed mechanisms and adverse effects

Drug	Proposed mechanism of action	Adverse effects
Oral therapy		
Tocopherol (vitamin E)	Antioxidant effect, DNA repair, immune modulation	Nausea, vomiting, diarrhoea, fatigue, weakness, blurred vision
Para-aminobenzoate (Potaba®)	Enhancement of oxygen uptake, GAG secretion and monoamine oxidase activity	Nausea, anorexia, pruritus, anxiety, chills, cold sweats, confusion, difficulty concentrating
Colchicine	Reduction in lactic acid production by leukocytes, decreased activity of phagocytosis, anti-inflammatory effect	Nausea, vomiting, bone marrow depression (aplastic anaemia, agranulocytosis or thrombocytopenia), peripheral neuritis
Tamoxifen	Modulation of TGFβ secretion from fibroblasts	Hypercalcaemia, peripheral oedema, depression, dizziness, headache
Propoleum	Unknown	Skin irritation (rash, pruritus, erythema, oedema)
Acetyl-L-carnitine	Unknown	Nausea, vomiting, diarrhoea
Injection therapy		
Corticosteroids	Anti-inflammatory effect, inhibition of phospholipase A_2, immune suppression	Local tissue atrophy, thinning of skin, systemic effects rarely seen
Orgotein	Conversion of superoxide radicals to H_2O_2 and O_2, anti-inflammatory effect	Pain, oedema, stiffness, dysaesthesias, skin rash
Collagenase	Degradation of interstitial collagens	Injection-site pain, ecchymosis, corporal rupture
Verapamil	Inhibition of calcium-dependent transport of extracellular matrix molecules (collagen, fibronectin, GAGs), increased collagenase activity, modification of inflammatory response, inhibition of fibroblast proliferation	Nausea, lightheadedness, penile pain, ecchymosis, no cardiovascular events reported
Interferon-α-2a or -2b	Regulation of immune response, inhibition of fibroblast and collagen production	Myalgias, arthralgias, sinusitis, fevers, flu-like symptoms

GAG = glycosaminoglycan; **TGF**β = transforming growth factor-β.

investigators reported no statistical differences between the treatment groups, but interestingly were able to conclude that patients who had plaque lengths ≤20mm at baseline had a 100% resolution of symptoms at 2 years post-presentation, while those with plaque lengths >20mm experienced only a 20% resolution rate.

Despite the lack of definitive evidence for tocopherol in the treatment of Peyronie's disease, urologists commonly prescribe this agent at doses of 400IU, once or twice daily, because of its wide availability, low cost and minimal to absent adverse effects. Additionally, as many patients with Peyronie's disease experience psychological effects, tocopherol may also serve to provide a psychological placebo benefit to patients wishing to do something (as opposed to nothing) to alter the course of their disease.

3.2 Para-Aminobenzoate (Potaba®)

Para-aminobenzoate (Potaba®) is a compound that was introduced in 1959 as a possible therapy for Peyronie's disease after it was shown to decrease collagen production *in vitro* when added to fibroblast cell cultures.[23] Its mechanism of action is hypothesised to involve the enhancement of three endogenous antifibrotic properties of tissues: oxygen uptake, glycosaminoglycan (GAG) secretion and monoamine oxidase activity. Monoamine oxidase is known to break down circulating monoamines that include adrenaline, noradrenaline (epinephrine, norepinephrine), dopamine and serotonin. Therefore, increased monoamine oxidase activity decreases serotonin, which may play a role in preventing fibrogenesis.

Despite its long history of use, human study data on the efficacy of para-aminobenzoate for Peyro-

nie's disease are limited. Weidner et al.[24] recently conducted a prospective, placebo-controlled, double-blinded, randomised study in which 103 patients with Peyronie's disease were administered either para-aminobenzoate (3g four times daily) or placebo over a 12-month period. Patients were required to have had Peyronie's disease for <12 months, with non-calcified plaques, and to have received no prior treatments. Their results revealed that 74.3% of the para-aminobenzoate-treated group and 50% of patients in the placebo group experienced a beneficial response, which was defined as a regression in plaque size and/or a reduction in penile curvature ≥30%. Patients receiving para-aminobenzoate had a mean plaque regression from 259mm^2 to 142mm^2, while mean plaque area in the placebo group decreased from 259mm^2 to 233mm^2. No significant improvement in penile pain or change to the pre-existing curvature was noted. The authors concluded that para-aminobenzoate exerted a protective effect against progression of penile curvature and recommended its use as an agent to stabilise and prevent further advancement of Peyronie's disease.

Currently, para-aminobenzoate is considered to be a first-line therapy for Peyronie's disease because it is a well tolerated, inexpensive and effective drug. Its adverse effect profile is minimal, with nausea and anorexia occurring most frequently. A recent German questionnaire study of 636 urologists treating Peyronie's disease revealed that the majority of their patients (76%) were treated with either para-aminobenzoate (46%) or tocopherol (29%).[25] Since additional double-blinded, placebo-controlled experiments are lacking, formal recommendations for use of para-aminobenzoate in Peyronie's disease have not been established to date.

3.3 Colchicine

Colchicine is a medication that is commonly employed in the treatment of acute attacks of gout. Its exact mechanism of action in Peyronie's disease is unknown but is hypothesised to involve a reduction in lactic acid production by leukocytes (thus leading to decreased uric acid deposition) and decreased phagocytosis (with resultant anti-inflammatory effects). It is postulated that the anti-inflammatory properties of colchicine may decrease collagen synthesis and upregulate collagenase activity.

The efficacy of colchicine in Peyronie's disease was evaluated in a rat model using tunical TGFβ injections to induce a pro-fibrotic state.[26] Two groups of rats were divided into three treatment subgroups: water (control), ibuprofen and colchicine. The first group of rats received treatment soon after initial TGFβ injection, while the second group waited 6 weeks into the disease process. Results showed that rats receiving colchicine soon after TGFβ injection exhibited less collagen deposition and reduced elastic fibre fragmentation compared with the other groups. Colchicine-treated rats also experienced a downregulation of TGFβ expression compared with the other treatments. These results suggest that colchicine may provide a benefit if given early in the disease process; however, the criticism is that this Peyronie's disease-like state may not be the same disease entity as Peyronie's disease.

Kadioglu et al.[27] examined the efficacy of colchicine administered to 60 men with Peyronie's disease presenting in the acute phase of the disease process. Patients had a mean disease duration of 5.7 ± 4.3 months at the time of treatment, and results at follow-up (10.7 ± 4.7 months later) showed improvement in penile deformity in 30% of men, no improvement in 48.3%, deterioration in 21.7% and resolution of pain in 95%. The authors concluded that the best results were observed in patients exhibiting no vascular risk factors or erectile dysfunction, those presenting within 6 months of disease onset and patients with <30° of curvature. As this study lacked appropriate controls, few conclusions can be drawn from it about the efficacy of colchicine in patients with Peyronie's disease. Additionally, the results reported in this study are similar to the percentages documented in studies of the natural history of Peyronie's disease. However, the data do support the claim that colchicine is more likely to have a greater benefit when employed early in the disease process.

A similar study[28] divided patients with Peyronie's disease of <6 months duration into treatment groups that received either ibuprofen or a combination of tocopherol and colchicine. Compared with ibuprofen alone, subjects receiving combined therapy with tocopherol and colchicine were found to have significantly smaller plaque sizes and angles of penile curvature. The investigators recommended use of colchicine and tocopherol in the early stages of Peyronie's disease in men without erectile dysfunction and with <30° of penile curvature, in an attempt to stabilise the disease process. This study was hindered by the lack of an appropriate control group as well as objective measurements of plaque dimensions and penile curvature.

A recent, randomised, double-blinded, placebo-controlled study evaluated the efficacy of colchicine in Peyronie's disease examined 84 patients who presented with a mean disease duration of 15 months.[29] Patients were randomised to receive either colchicine 0.5–2.5mg every day for 4 months or placebo over the same time period. PDDU and IIEF scales were used to assess status objectively. No significant differences between study groups in measured curvature angles, plaque sizes or pain experienced were documented. Although this study appears to conclusively rule out colchicine as an effective therapy in Peyronie's disease, the patients examined had a mean duration of disease of 15 months, and, as shown by Kadioglu et al.,[27] colchicine therapy was not likely to have shown a significant benefit in such a group.

To date, there is no general consensus regarding the use of colchicine in the treatment of Peyronie's disease. The efficacy of treatment increases when the drug is given to patients with fewer vascular risk factors, no co-morbid erectile dysfunction, less significant curvature (<30°) and those presenting early in their disease process. Colchicine, when administered in a regimen of 500mg three times daily, is most commonly associated with adverse gastrointestinal effects (nausea, vomiting, diarrhoea) but is generally considered to be a safely used medication for the long term.

3.4 Tamoxifen

Tamoxifen is a nonsteroidal, estrogen-receptor antagonist that is most commonly employed in patients with estrogen-receptor positive breast carcinoma. One proposed mechanism of action in patients with Peyronie's disease is modulation of TGFβ secretion from fibroblasts.

Tamoxifen was first used as a potential treatment therapy for Peyronie's disease in a 1992 study that treated 32 patients with Peyronie's disease with tamoxifen 20mg twice daily over a 3-month period.[30] Tamoxifen improved penile pain in 80% of subjects, reduced erectile deformity in 35.5% and was associated with plaque shrinkage ≥1cm in 34.3% of patients. Greater improvement was observed in patients who were in earlier stages of Peyronie's disease (<4 months) than in those receiving treatment later in the disease process.

However, the efficacy of tamoxifen in Peyronie's disease was called into question by the results of a 25-patient, placebo-controlled study of tamoxifen 20mg twice daily for 3 months.[31] Investigators used penile radiography, ultrasound and pharmacologically induced erection (using alprostadil [prostaglandin E_1]) to objectively compare baseline status prior to treatment with follow-up 4 months later. No statistically significant differences between tamoxifen and placebo with respect to decreased penile pain (66.6% vs 75%, respectively), reduction in penile deformity (46.1% vs 41.7%, respectively) or decrease in plaque size (30.7% vs 25%, respectively) were observed. Critics of the study point out that patients with Peyronie's disease would probably have experienced better results had they received tamoxifen treatment earlier in the course of their disease. However, in the absence of more conclusive data demonstrating a beneficial effect of tamoxifen on Peyronie's disease, this drug cannot be recommended for routine treatment in patients with Peyronie's disease.

3.5 Propoleum

Information regarding the composition, mechanism of action and efficacy of propoleum is limited, as the substance is patented in Cuba and its use

restricted to that country. Propoleum came into use after a Cuban patient with Peyronie's disease began taking the substance for giardiasis and noted that his Peyronie's disease had improved. The only published efficacy information is provided in four articles by the same group of researchers in Cuba. In their first published report, Lemourt et al.[32] studied 34 patients with Peyronie's disease and reported a 5-fold reduction in plaque consistency among those treated with propoleum over a 6-month period in a controlled, double-blinded, clinical trial. However, the investigators noted that no changes on ultrasound were seen in the control group, which is not consistent with the natural history of Peyronie's disease.

A second, uncontrolled study involved 13 patients with Peyronie's disease who received propoleum and were followed-up at 6 months for evaluation of pain, curvature and plaque size.[33] In this study, 77% of patients experienced improvement in penile curvature and penile plaques were reduced by 0.64cm on average (with 23% showing complete resolution).

As there is little information regarding the properties of propoleum, and the substance cannot be obtained outside of Cuba, clinical knowledge of this drug is limited. Appropriately designed, placebo-controlled, double-blinded efficacy studies performed by additional research groups are necessary to support or dispute currently published findings.

3.6 Acetyl-L-Carnitine

To date, only one study has been conducted to evaluate the efficacy of acetyl-L-carnitine. In this randomised study involving 48 patients with Peyronie's disease, subjects were given either tamoxifen 20mg twice daily or acetyl-L-carnitine 1g twice daily for 3 months.[34] Penile curvature, plaque size and pain were assessed using PDDU. Results comparing acetyl-L-carnitine with tamoxifen showed that acetyl-L-carnitine was significantly more effective than tamoxifen at reducing pain (92% vs 50%, respectively) and inhibiting disease progression (92% vs 46%, respectively), while both drugs were shown to significantly reduce mean plaque size (from 116.5 to 89.6mm^2 with tamoxifen vs 109.8 to 61mm^2 with acetyl-L-carnitine). Only acetyl-L-carnitine was shown to significantly reduce mean penile curvature (from 15.9 to 8.9°). Although no control was provided in the study, since tamoxifen has been previously shown to be similar to placebo, it can be inferred that acetyl-L-carnitine is possibly effective at reducing pain and at decreasing overall disease progression in patients with Peyronie's disease. The efficacy of acetyl-L-carnitine in reducing plaque size and curvature could not be determined from this study, as the drug was not directly compared with a control (and thus not compared against the natural history of Peyronie's disease); however, both outcomes were reported as having changed statistically significantly from baseline with acetyl-L-carnitine.

Adverse effects with acetyl-L-carnitine are uncommon but may include nausea, vomiting and diarrhoea. Further studies are required to provide more conclusive evidence of the efficacy of acetyl-L-carnitine in patients with Peyronie's disease.

4. Intralesional Pharmacotherapy

In addition to oral treatments for Peyronie's disease, another option for conservative therapy is injection of pharmacologically active agents directly into penile plaques (figure 1). One advantage of

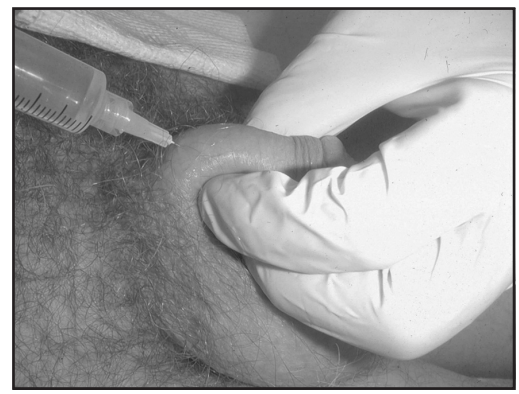

Fig. 1. Image demonstrating intralesional injection technique. Following administration of a penile block with 1% lidocaine (lignocaine) [without epinephrine (adrenaline)], penile lesions are repeatedly infiltrated with the selected pharmacotherapy using a 1.27cm (0.5 inch), 25-gauge needle.

intralesional treatment compared with oral treatment is localised delivery of a particular agent, which provides higher concentrations of the drug than might be tolerated if given systemically. Several drugs have been used to treat penile plaques with varying degrees of efficacy, including corticosteroids, orgotein, collagenases, verapamil and interferon-α-2a or -2b. Each of these agents will be described in greater detail in sections 4.1–4.5. Figure 1 demonstrates the appropriate method of intralesional injection therapy administration.

4.1 Corticosteroids

Corticosteroids are candidates for treatment of Peyronie's disease because of their anti-inflammatory effects via inhibition of phospholipase A_2 and suppression of the immune response.[35] The first documented use of intralesional corticosteroids for Peyronie's disease was reported by Bodner et al.[36] who, in 1953, reported a decrease in plaque size and penile pain following dexamethasone injection. A second study[37] of 21 patients with Peyronie's disease conducted in 1975 failed to confirm these earlier findings even though a high percentage of the patients who had previously failed other therapies noted decreased pain and plaque size. These investigators concluded that the results with intralesional corticosteroid injection did not differ significantly from what would be expected from the natural history of the disease.

More promising results were seen in a study evaluating the efficacy of injected triamcinolone hexacetonide (a longer-acting corticosteroid) in 42 patients with Peyronie's disease who had failed to show resolution of disease 1 year after initial presentation.[38] These investigators noted that 33% of patients had complete or marked improvement of symptoms and concluded that best responses were seen in younger patients with small, firm, discrete plaques located in the distal penis. However, the only randomised, single-blinded, placebo-controlled study of intralesional injection with a corticosteroid (betamethasone) failed to show a statistically significant improvement in treated patients.[39]

Because of the lack of conclusive evidence showing benefit and because of the adverse effects experienced with long-term use of corticosteroids (e.g. local tissue atrophy, thinning of skin, immune suppression), corticosteroid injections are not currently advocated as an intralesional therapy for Peyronie's disease.

4.2 Orgotein

Orgotein is a pharmaceutical version of copper/zinc superoxide dismutases that possesses anti-inflammatory properties. Superoxide dismutase occurs physiologically in cells such as polymorphonuclear leukocytes and generates large amounts of superoxide radicals for various biological purposes, including the destruction of foreign materials (tissue, bacteria). Through its actions, superoxide radicals are converted to the more benign H_2O_2 and O_2 molecules. As superoxide radicals have the potential to further exacerbate inflammation and generate fibrosis, it was hypothesised that orgotein might potentially reduce the fibrosis associated with Peyronie's disease.

Although orgotein had been used in the treatment of inflammatory urinary tract conditions as early as 1974, its first use as an intralesional injection in patients with Peyronie's disease was not until 7 years later. Two independent studies involving a total of 45 patients found that patients treated with orgotein exhibited decreases in penile pain, curvature and plaque size, and 19 of 22 patients who previously were unable to engage in sexual activity displayed marked improvement, with some experiencing a complete restoration of normal erectile function.[40,41] However, these preliminary studies were limited by lack of appropriate controls and flawed experimental design.

Although additional uncontrolled studies have since reported the beneficial effects of intralesional orgotein, no randomised, placebo-controlled, double-blinded studies have been published to date that clearly identify a statistically significant effect of this therapy.[42,43] Adverse effects reported for orgotein include pain, swelling, stiffness, dysaesthesias and skin rashes.[44] As information on orgotein

is limited, in part by its restricted use in the US because of reported toxicity with off-label use, it is unlikely to be prescribed for the intralesional therapy of Peyronie's disease.

4.3 Collagenase

Collagenases are physiological enzymes (also classified as specific matrix metalloproteinases 1, 8, and 13) that are capable of degrading interstitial collagens, such as type II collagen. Gelbard et al.[45] were the first to examine the effect of collagenases on Peyronie's disease plaques. These investigators utilised highly purified clostridial collagenases (PCCs) to test their effect on various human tissues *in vitro*, including human pericardium, human corpus cavernosum, tunica albuginea and Peyronie's disease plaques. Results from these experiments demonstrated a considerable reduction in the size of the Peyronie's disease plaque, along with microscopic fraying and dispersal of collagen bundles, when compared with plaques injected with normal saline. Predictably, elastic fibres, vascular smooth muscle and axonal myelin sheaths were not affected by collagenase application.

Following up on these *in vitro* results, this research team performed an *in vivo* pilot study that involved injecting intralesional PCC (mean dose 2328 units) in 31 men with Peyronie's disease.[46] After 4 weeks of treatment, 65% of patients exhibited objective improvement, 93% reported elimination of pain, and the ability to have intercourse was restored in three of four patients. Additionally, the researchers noted that penile plaques were either altered significantly or absent in four patients and reduced by 20–100% in 16 others.

In 1993, the same research team conducted a randomised, double-blinded, placebo-controlled study of intralesional PCC in 49 men with Peyronie's disease.[47] Study participants were allocated to one of three groups according to disease severity: group 1 included men with curvature <30° or a palpable plaque <2cm in length; group 2 consisted of men with curvature of 30–60° or those with plaques 2–4cm in length; and group 3 were men exhibiting the most severe disease with curvature >60° and/or plaques >4cm in length. Groups 1, 2, and 3 were treated with 6000, 10 000 and 14 000 units of PCC, respectively, and were evaluated at a 3-month follow-up. Positive responses to PCC were seen in 100% of group 1, 36% of group 2 and 13% of group 3 patients compared with 25%, 0% and 0% in placebo groups, respectively. Overall comparisons between the treatment and control arms demonstrated a statistically significant improvement in patients receiving PCC intralesionally.

Interestingly, a study evaluating the presence of IgG antibodies to collagenase in healthy men versus those with Peyronie's disease found that antibodies were present in 34% of healthy men versus 58% of men with Peyronie's disease.[48] These data suggest the possibility that collagenase activity is upregulated in patients with Peyronie's disease or that effective collagenase activity is decreased because of an autoimmune response against the protein.

PCC injections are associated with adverse effects that include injection-site pain, ecchymosis and corporal rupture, although such effects were generally noted in only a small percentage of patients.

Because of its documented efficacy, intralesional collagenase therapy has been used to treat patients with Peyronie's disease; nevertheless, further studies are necessary to confirm a beneficial response to PCC. A multicentre, controlled study is currently awaiting initiation in the US.

4.4 Verapamil

Verapamil is a calcium channel antagonist that is thought to selectively inhibit calcium ion flux in both cardiac muscle and cells responsible for intracardiac conduction, as well as coronary and systemic arteries. The rationale for its use in the intralesional treatment of patients with Peyronie's disease is based on *in vitro* data that demonstrate that transport of extracellular matrix molecules that include collagen, fibronectin and GAGs is a calcium-dependent process.[49] In addition to resulting in decreased intracellular calcium, verapamil has been shown to increase collagenase activity, affect cytokine expression associated with early inflammation and

wound formation, and inhibit *in vitro* fibroblast proliferation in Peyronie's disease plaques.[49,50]

Use of intralesional injections of verapamil in patients with Peyronie's disease was popularised by Levine et al.,[51] who showed in a non-randomised, uncontrolled study that bi-weekly injections of verapamil given over a 6-month period led to subjective decreases in penile narrowing (reported by 100% of patients) and decreases in curvature (among 42% of patients) and objective decreases in plaque volume of ≥50% demonstrated in 30% of patients. Patients also reported benefits with respect to plaque softening and erectile function.

Additional uncontrolled studies (involving up to 156 participants) evaluating the efficacy of 12 injections of verapamil (10mg in 10mL solution) given at 2-weekly intervals have similarly reported decreased penile pain (percent patients 90.9–100%), decreased curvature (percent patients 10.2–60%, with improvement being inversely associated with disease duration), increased girth (percent patients 83%), increased rigidity (percent patients 80%), reduction in penile deformity (percent patients 86%), improved erectile function (percent patients 71–72%) and subjective softening of plaque (percent patients 48.7%).[52-54]

Rehman et al.[55] conducted the only randomised, placebo-controlled, single-blinded study of verapamil. This study included 14 patients with Peyronie's disease and consisted of weekly injections of verapamil or placebo for 6 months with pre- and post-treatment PDDU used to objectively measure results. Comparing verapamil with placebo, the data obtained showed statistically significant decreases in mean plaque volume (57% vs 28%, respectively), statistically significant improvements in mean plaque-associated penile narrowing, statistically significant subjective improvements in mean erectile function (42.87% vs 0%, respectively) and subjective softening of plaques in verapamil-treated patients. The mean change in penile curvature with verapamil was not statistically significant (reduction from 37.71° at baseline to 29.57°; $p < 0.07$).

Published data on verapamil consistently demonstrate its beneficial effects when injected intralesionally in patients with Peyronie's disease. Adverse effects of the therapy that have been reported thus far include nausea, lightheadedness, penile pain and ecchymosis. No cardiovascular events have been documented, and the adverse effects of verapamil are generally considered to be mild. As only one study evaluating the efficacy of verapamil has included a placebo arm, additional studies are required to more fully document the benefit of verapamil in terms of altering the natural history of Peyronie's disease.

4.5 Interferon-α-2a or -2b

Interferons are a class of endogenously produced, low molecular weight cytokines that function to regulate the normal immune response to foreign antigens. Currently, three types of natural interferons have been identified: α, β and γ. The first suggested use of interferons for the treatment of Peyronie's disease was initiated by Duncan et al.,[56] who treated cultured fibroblasts derived from Peyronie's disease plaques with a human recombinant interferon. Results showed that while the α, β and γ forms of interferon led to inhibition of fibroblast and collagen production, interferon-γ also caused an increase in GAG and fibronectin production. From these data, the authors hypothesised that interferon-α and -β were reasonable agents for use as intralesional therapies for Peyronie's disease.

The following year, a German group tested the efficacy of five injections of interferon-α-2b (1MU) given over 1-week intervals in 25 patients with Peyronie's disease.[57] Objective measurement of Peyronie's disease plaque size was obtained by ultrasonography prior to and 1 and 6 months after treatment with interferon. Clinically, no patients exhibited progression of disease and one showed improvement. Plaque size decreased in seven cases (patients with minimal to no plaque calcification at baseline), remained stable in 12 cases, and increased in six cases (patients with pre-existing calcified plaques). On the basis of these observations, the research group hypothesised that interferon therapy is optimally initiated early on in the disease process before calcification occurs.

Another uncontrolled study that involved 20 patients with Peyronie's disease receiving interferon-α-2b utilised PDDU and questionnaires to assess penile blood flow, curvature, plaque size and perceived sexual function.[58] Patients were given interferon-α-2b 1MU at 2-week intervals over a period of 6 months with evaluations taken prior to initiation of therapy and after 6 months of treatment. All patients reported subjective softening of their plaques and nine of nine patients reported resolution of penile pain. Sixty-five percent of subjects exhibited significant improvement (ranging from 20–90%) in curvature, and 85% were found to have 10–80% decreases in plaque size. All results were found to be significant compared with baseline. Additional uncontrolled studies have reported similar findings of efficacy in patients receiving interferon therapy.[59,60]

The first placebo-controlled study involving interferon-α-2b was conducted in 1997 by Judge and Wisniewski,[61] who examined the effects of interferon 1.5MU administered intralesionally three times weekly over a 3-week period in 13 patients with Peyronie's disease of ≥12 months duration. These investigators found that six of ten patients achieved complete resolution of erectile discomfort and significant improvements in penile deformity (mean improvement 20°), with those presenting with smaller initial plaque lengths (<4cm) showing the greatest improvements. One interesting study that employed magnetic resonance imaging (MRI) to quantitatively assess plaque size in patients with Peyronie's disease prior to and following treatment with interferon-α-2a supported the finding that interferon therapy was more likely to benefit patients presenting with smaller plaques.[62] Among subjects classified as having plaques 0.5–1cm in length, complete resolution (at least below the resolution capacity of MRI) was seen, while those with plaque lengths of 1.5 and 2cm achieved mean 90% and 83.3% plaque reductions, respectively.

More recently, Dang et al.[63] conducted a crossover study in which 7 of 21 patients received placebo injections for 6 weeks, followed by interferon-α-2b 2MU treatment after a 1-month washout period, while the remaining patients received interferon therapy only. Objective evaluations of curvature, blood flow and degree of erectile dysfunction were obtained using PDDU and IIEF questionnaires. Results demonstrated ≥20% improvement in curvature in 67% of men, decreased penile pain in 80%, subjective decrease in plaque size in 71%, and improvement in erectile function in 71% of patients with moderate to severe erectile dysfunction at baseline. Statistically significant improvements were noted in penile pain and curvature. In a follow-up study from the same institution, Kendirci et al.[64] further demonstrated that interferon-α-2b resulted in a significant benefit on penile haemodynamic parameters, as demonstrated on PDDU.

The most scientifically definitive study to date on the efficacy of intralesional interferon-α-2b in Peyronie's disease is a single-blinded, multicentre, placebo-controlled, parallel study involving 117 patients published in 2006.[65] Fifty-five patients were given interferon-α-2b 5MU at 2-week intervals over a period of 12 weeks, and each patient was evaluated for penile curvature, plaque characteristics (size, density), penile pain, erectile function, and penile haemodynamics using PDDU and IIEF questionnaires. Significant improvement was seen in actively treated patients compared with placebo for mean penile curvature (reduction from 49.9 to 36.4° in the interferon group vs 50.9 to 46.4° in the placebo group), mean penile plaque size (reduction from 4.8 to 2.2cm^2 in the interferon group vs 4.5 to 3.6cm^2 in the placebo group), mean plaque density (reduction from 2.29 to 1.52 in the interferon group vs 2.07 to 1.84 in the placebo group [range 0–3 for both groups]), pain resolution (67.7% of patients in the interferon group vs 28.1% of patients in the placebo group) and penile blood flows, while mean IIEF scores were not significantly different before and after treatment (interferon 18.32–20.80 vs placebo 17.98–19.05). These results provide the best efficacy evidence to date supporting use of interferon in patients with Peyronie's disease.

Injections with interferon-α-2b have been associated with mild to moderate adverse effects such as myalgias, arthralgias, sinusitis and flu-like symp-

toms, including fevers >38°C for the first 24 hours.[66] These adverse effects are for the most part well tolerated, especially when patients are premedicated with NSAIDs. Use of intralesional interferon-α-2b is becoming more popular in clinical practice for the treatment of patients with Peyronie's disease, as it is considered to be minimally invasive, has a favourable adverse effect profile, and is associated with proven disease outcome benefits. Uncertainties about the most effective concentration and frequency of administration continue to be investigated. As with intralesional verapamil therapy, interferon treatment is commonly employed by urologists as a therapeutic option for the treatment of Peyronie's disease.

5. Transdermal Pharmacotherapy

In addition to oral and injection routes of drug delivery, topical and transdermal approaches to the treatment of Peyronie's disease have been investigated. Topical preparations of β-aminopropionitrile, hydrocortisone and verapamil have been reported in uncontrolled trials to have effects ranging from none to significant reductions in pain, penile deviation and size of Peyronie's disease plaques.[67,68] However, the true efficacy of topical preparations was called into question following a 2002 study conducted by Martin et al.,[69] in which verapamil levels were measured in excised samples of tunica albuginea following two applications of topical verapamil. This study showed that verapamil was not present in any of the tunical samples obtained but was recovered in small amounts in the urine. Despite minimal systemic absorption, the lack of demonstrable verapamil in sampled tunica albuginea suggests that there is no scientific basis for its use. As such, topical therapies are not currently routinely employed in the treatment of Peyronie's disease.

To overcome limitations of topical therapies, emphasis has more recently been placed on testing modalities such as iontophoresis, which enhances the local uptake of drugs. Iontophoresis involves the application of an external electric force to induce further (electromotive) penetration of topical medication and has been evaluated to date with topical verapamil, dexamethasone and orgotein.[70] In contrast to the study by Martin et al.,[69] which demonstrated no uptake of verapamil in tunica albuginea following topical application, Levine et al.[71] reported that 71.5% of excised tunica albuginea samples from 14 men who received iontophoresis and topical verapamil therapy prior to undergoing surgical treatment for Peyronie's disease were found to contain measurable levels of verapamil. A subsequent prospective, controlled study evaluated the efficacy of electromotive verapamil and dexamethasone versus electromotive lidocaine (lignocaine) in 96 men with Peyronie's disease.[72] Men were randomised to receive either verapamil 5mg ± dexamethasone 8mg or 2% lidocaine with a 2.4mA electric current for 20 minutes, four times weekly for 6 weeks. Compared with baseline, significant decreases in median plaque volume (reduction from 824 to 348mm^3) and penile curvature (reduction from 43 to 21°) were seen in the actively treated groups whereas no changes in plaque volume or curvature were seen in the control group. Significant pain relief was experienced transiently in the control group and permanently in the treatment arm. These results support those of a previous, uncontrolled study that reported plaque reduction in 82%, curvature decrease in 84%, and pain elimination in 88% of 49 men who received verapamil and dexamethasone treatment with iontophoresis.[73]

6. Surgical Options

The objective of the current article is to focus predominantly on available pharmacological managements of Peyronie's disease; however, brief mention will also be made of surgical options that are available for men with this condition.

Surgical correction is indicated for patients who experience significant penile deformity that precludes sexual intercourse. Typically, these men will have previously received treatment with more conservative therapies, including oral and intralesional injections, and will have been given sufficient time (>12 months according to most authorities) for their plaque to mature and stabilise. When surgery is indicated, urologists may choose from a variety of

techniques that can be divided into two categories: reconstructive surgery or penile prosthesis implantation with or without remodelling. The decision as to which surgical procedure is to be performed is made at the urologist's discretion and will depend on the patient's clinical history, objective findings (severity of the angle of deformity, degree of preserved erectile function etc), and the surgeon's familiarity, experience and expected long-term results with the available procedures.

6.1 Reconstructive Surgery

Nesbit procedures have been practiced in association with Peyronie's disease for almost 30 years and involve a circumcision-like incision and plication of the non-involved side to effect a straightening of the penis. While this is a relatively easy procedure to perform, it may lead to post-operative shortening of the penis and is therefore typically reserved for patients with <60° deformity.[74] For patients with >60° deformity and concomitant erectile dysfunction, implantation of a penile prosthesis is more commonly performed.

Other options for reconstructive surgery include plaque excision with dermal grafting or plaque incision with insertion of a venous graft. To date, plaque excision has produced disappointing results with one study[75] demonstrating good results in only 35% of patients who were followed up 10 years after the procedure and a second study[76] reporting complications of erectile dysfunction in 20% and the need for further surgery in 17% of patients. Plaque incision involves a more extensive surgical dissection including mobilisation of Buck's fascia, harvesting of the long saphenous vein, and grafting of the resultant vein into the incised plaque. This procedure has resulted in better outcomes than excision, with a straightening of the penis occurring in 75–96% of reported cases, and a lower percentage of patients experiencing associated co-morbidities such as penile shortening or erectile dysfunction.[77,78]

6.2 Penile Prosthesis

Insertion of a penile prosthesis performed with or without manual modelling is usually reserved for patients with Peyronie's disease and severe erectile dysfunction, and is effective at straightening the penis in the majority of patients over time and restoring some degree of erectile function.

Although surgical procedures such as implantation of a penile prosthesis are usually the most risky, all operations are associated with possible infection, blood loss, discomfort and recurrence of Peyronie's disease plaque.

7. Future Perspectives

Several agents have demonstrated results *in vitro* that provide a theoretical basis for their possible use in Peyronie's disease in the future. Pentoxifylline, a non-specific cyclic adenosine monophosphate-phosphodiesterase (cAMP-PDE) inhibitor that has been approved for use in the treatment of intermittent claudication, has been shown to decrease the expression of collagen-I and α-smooth muscle actin (a myofibroblast marker) in human fibroblast cultures.[79] Similar findings have been observed with application of sildenafil together with L-arginine. Mechanistically, these findings can be explained by the observation that inducible nitric oxide synthase (iNOS) is expressed in human Peyronie's disease plaques, and inhibition of iNOS leads to a significant exacerbation of tissue fibrosis. As the cyclic guanosine monophosphate (cGMP) and cAMP pathways are known to regulate iNOS, pharmacological agents that modify cGMP or cAMP levels will hypothetically alter iNOS levels. Data published in two abstracts provide further support for this concept.[80,81] In one of these,[80] pentoxifylline demonstrated an antifibrotic effect on fibroblasts cultured from patients with Peyronie's disease; in the other,[81] rats treated with inducible nitric oxide synthase gene therapy in an animal model of Peyronie's disease experienced regression of their Peyronie's disease plaques. However, use of pentoxifylline as a therapeutic agent for the treatment of Peyronie's disease has been reported in only one

Table III. Summary of placebo-controlled studies examining the efficacy of available oral and injection therapies for patients with Peyronie's disease (PD)[a]

Drug	Patients (n)	Mean pain improvement (%)	Mean decrease in plaque size	Mean decrease in penile curvature	Patients reporting improvement in sexual function (%)	Patients reporting progression of PD (%)	Reference
Oral therapy							
Tocopherol (vitamin E)	40	35	NS	NS	NA	NA	21
Para-aminobenzoate (Potaba®)	103	NS	259 to 142mm^2 (259 to 233mm^2)	NS	NA	2.9 (32.5)	24
Colchicine	84	NS	NS	NS	NS	NS	29
Tamoxifen	25	NS	NS	NS	NA	NA	31
Propoleum[b]	34	Yes	2×	Yes	NA	NA	32
Acetyl-L-carnitine[c]	48	92 (50)	NS	NS	NA	8 (54)	34
Injection therapy							
Corticosteroids	30	NS	NS	NS	NA	NA	39
Collagenase	49	NA	Yes	Yes	NA	NA	47
Verapamil	14	NA	57% (28%)	NS	42.9 (0)	NA	55
Interferon-α-2b	13	67	67%	60% with ~20° mean	67	NA	61
	21	80	NS	67% with 25° mean	71	NA	63[d]
	117	67.7 (28.1)	4.8 to 2.2cm^2 (4.5 to 3.6cm^2)	49.9 to 36.4° (50.9 to 46.4°)	NS	NA	65

a Only results that are statistically significant ($p < 0.05$) compared with placebo are listed. Placebo values (when available) are listed in parentheses.

b Use of propoleum is restricted to Cuba and all published reports originate from the same group of researchers. The study design used is questionable.

c Study compared acetyl-L-carnitine with tamoxifen (not placebo); however, since tamoxifen has been shown to be equal to placebo, results are included for comparison purposes.

d Study was a cross-over design with half of patients receiving placebo for 6 weeks followed by interferon treatment.

NA = not addressed by study; **NS** = not significant.

published case report[82] and more definitive evidence of its efficacy in this setting is lacking.

8. Conclusions

Peyronie's disease is a common disorder that often presents with any combination of penile pain, curvature, penile plaque or erectile dysfunction. The disorder may have an underlying genetic predisposition and become manifest with an inciting event, such as trauma. Following the initial evaluation of a patient presenting with Peyronie's disease, the recommended standard of care involves an initial trial of oral and/or intralesional pharmacotherapy in the acute phase (first year) of this condition.

Among available oral treatments, tocopherol and para-aminobenzoate are the most commonly prescribed agents as they are inexpensive, have a mild adverse effect profile and provide a psychological placebo benefit. Colchicine, tamoxifen, propoleum and acetyl-L-carnitine are additional oral therapies that are also occasionally prescribed in other countries and are still considered investigational in nature. Oral treatments are more likely to be successful if initiated early in the course of a patient's disease and for the most part prevent progression rather than curing the condition.

Intralesional injection therapies have become more popular over the last two decades and provide an additional, minimally invasive modality for patients with Peyronie's disease. The intralesional approach allows for direct delivery of a particular agent at concentrations that might otherwise be toxic systemically. Use of corticosteroids or orgotein is not currently recommended, and there have been no randomised, placebo-controlled studies clearly documenting their efficacy. Use of collagenase is supported by the results of studies that have revealed significant benefits for this therapy when employed early in the course of Peyronie's disease. Verapamil has been shown in one placebo-controlled and numerous uncontrolled studies to have beneficial effects in Peyronie's disease, but additional, controlled studies are required to further validify its use. Interferon-α-2a or -2b has been reported in peer-reviewed studies to have efficacy in improving penile curvature, plaque size and density, and to reduce penile pain in several well controlled studies. Table III summarises the results of several placebo-controlled studies evaluating the efficacy of oral and intralesional therapies for Peyronie's disease.

Surgery is reserved for patients with Peyronie's disease who are unable to have sexual intercourse and who have failed conservative therapy with oral and/or intralesional agents. Surgical procedures that are commonly used in patients with Peyronie's disease include plication, plaque incision/excision with or without grafting, and implantation of an inflatable penile prosthesis.

As the definitive pathophysiology of Peyronie's disease has yet to be elucidated, further research is required in this area. Currently, oral pharmacotherapy has experienced negligible success in improving penile pain, curvature and plaque size in patients with Peyronie's disease. Intralesional therapy using various agents (e.g. verapamil and interferon) is growing in clinical acceptance and popularity as a minimally invasive approach for the treatment of Peyronie's disease. As our scientific understanding of the underlying mechanisms of this perplexing condition increase, we can anticipate the development of novel medical therapies for Peyronie's disease.

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Correspondence: Dr *Wayne J.G Hellstrom*, Section of Andrology, Department of Urology, Tulane University Health Sciences Center, 1430 Tulane Avenue, New Orleans, SL-42, LA 70112, USA.
E-mail: whellst@tulane.edu