
















# Non-Surgical Treatment Options for Peyronie's Disease

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## Abstract

Peyronie's disease, which occurs with the formation of a fibrous plaque in the tunica albuginea; is a disease that causes some physical problems such as bending and shortening of the penis. There are surgical treatment methods of this disease as well as non-surgical treatment methods. Non-surgical treatment methods, which are grouped under six headings: oral treatments, topical treatments, traction and vacuum treatments, shock wave therapy, intraplate injection treatments, and experimental treatments, can be preferred in cases where the symptoms are not very advanced because they provide advantages in terms of ease of application, accessibility, and cost. Although the only non-surgical treatment method approved by the FDA (U.S. Food and Drug Administration) yet is clostridium collagenase histolikum, which is used in intraplaque injection, studies have shown that other methods also reduce curvature, pain, and plaque volume.

**Keywords:** Peyronie's Disease, Non-Surgical Treatment, Plaque.

## INTRODUCTION

Fibrous plaque formation in the tunica albuginea layer surrounding the corpus cavernosum causes Peyronie's disease, although its pathological mechanism has not been fully elucidated. The disease was first described by Francois Gigot de La Peyronie in 1743. The disease, characterized by penile curvature, pain, erectile dysfunction, penile shortening, and deformity, has two phases, acute and chronic. While there is active inflammation in the acute

phase, the lesion stabilizes in the chronic phase. Plaque calcification occurs after the inflammatory response resulting from vascular damage in the tunica albuginea (1). In the tissue under the microscope, increased connective tissue and inflammatory cells are seen. The prevalence of the disease, which varies between 3.2% and 13% in studies, is generally seen in men between the ages of 50-60 (2). It should also be considered that patients may not apply to health institutions due to psychosocial or cultural reasons. While Peyronie's disease is associated with increased

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Dupuytren's contractures, plantar facial contractures (Ledderhose disease), tympanosclerosis, trauma, transurethral procedures, diabetes, gout, Paget's disease, and even beta-blocker use, the exact etiology is unknown. Still, penile trauma, genetic conditions, and genital system diseases thought that three main factors, including the history of the disease, increase the risk of the disease (3). In recent years, it has been stated that the increase in TGF- $\beta$  expression is also effective in its pathological mechanism (4). The treatment of this disease, which affects patients psychologically by causing problems such as lack of self-confidence, anxiety, and depression, in addition to physical problems very important for improving the quality.

Although surgical applications may be preferred in patients with advanced symptoms, non-surgical treatment options can be advantageous when conditions such as ease of application, easy accessibility, and cost are taken into account. In the guidelines published by the EAU (European Association of Urology) and AUA (American Urological Association), there are tables with suggestions about which method would be more beneficial to use, and studies are still being carried out on the effectiveness of these methods.

### Search strategy and selection criteria

Articles on non-surgical treatment methods in the treatment of Peyronie's disease have been reviewed and compiled, emphasizing being up to date. The therapeutic agents' efficacy was discussed with the summaries given at the end of each non-surgical treatment method.

## ORAL TREATMENT METHODS

### 1. Vitamin E

#### Mechanism

Acting as a natural antioxidant, vitamin E acts by reducing the number of oxygen-free radicals produced during cellular metabolism. Lipid peroxides are selective and potent inhibitors of prostacyclins. Vitamin E fulfills its antioxidant effect by preventing the peroxidation of lipid peroxides. It is still a popular treatment modality due to its low cost and relatively mild side effects (5, 6).

#### Evidence

In the first studies on vitamin E, a reduction in plaque size was reported in 91% of patients and decreased curvature in 78%. In the literature published between 1952-1982, there are 0-70% response rates when 200-800 mg of vitamin E is

used daily. At the NIH Conference on Peyronie's disease in 1993, Devine and Snow presented a study in which 105 patients taking oral vitamin E reported a 99% reduction in pain and a 13% reduction in penile curvature. No objective change was observed in 70% of the patients. Studies have shown that vitamin E affects reducing penile pain, and it affects penile curvature and plaque size relatively less (6, 7).

### 2. Colchicine

#### Mechanism

Colchicine is an alkaloid obtained from *colchicum autumnale*. It is an anti-inflammatory agent that inhibits collagen synthesis and stimulates collagenase activity. It has important effects in both the inflammatory and fibrotic stages of the disease.

#### Evidence

An uncontrolled study reported a slight reduction in curvature in 11%, a significant reduction in curvature in 26%, and a reduction in plaque size in 50%. However, there was no improvement in hourglass deformity and hardening. Levine reported that more than half of the more than 30 patients treated with colchicine had gastrointestinal disturbances (7, 8). Colchicine is used 2mg/day for 3-6 months in the treatment of Peyronie's disease. Studies have shown significant improvements in penile pain and curvature, with reduction or disappearance of penile plaques. Apart from gastrointestinal side effects, side effects such as fever, skin rashes, agranulocytosis, aplastic anemia, myopathy, and angioneurotic edema have also been observed (9).

Better results can be obtained when colchicine and vitamin E are used together. It has been reported to show significant improvement in plaque size and curvature, especially in early-stage disease (6, 10).

### 3. Phosphodiesterase Type 5 Inhibitors (PDE-5I)

#### Mechanism

Activation of the nitric oxide pathway by phosphodiesterase type 5 inhibitors (PDE5is) plays a role in improving erectile function, suppressing collagen synthesis, and initiating apoptosis of myofibroblasts (11).

#### Evidence

Long-term administration of PDE5i in animal experiments showed increased collagen and a decrease in fibroblasts

in tunica albuginea cells (12, 13). PDE5i was therefore investigated for its effects on plaque formation and remodeling in Peyronie's disease. In one study, 39 Peyronie's patients were administered daily sildenafil or vitamin E for three months. A similar reduction in plaque size was seen, but a statistically more significant improvement in pain reduction scores and erectile function was documented in the Sildenafil group compared to the vitamin E group (14). In another retrospective controlled study, 65 patients with isolated septal scars (ISS) without evidence of penile deformity were treated for six months without treatment. Follow-up and daily use of 2.5 mg tadalafil were compared. The resolution of septal scars was 10% and 69%, respectively, in the untreated and tadalafil-treated groups (15). Finally, a newer RCT, extracorporeal shock wave therapy, and a combination of tadalafil 5 mg once daily improved the erectile function score but significantly reduced penile curvature and plaque size. It was documented that it did not change significantly.

#### 4. Carnitine

##### Mechanism

Acetyl-L-carnitine and propionyl-L-carnitine, a derivative of carnitine, are inhibitors of acetyl coenzyme-A that help repair damaged DNA and prevent free radical formation during cell stress (16, 17).

##### Evidence

It has been shown that propionyl-L-carnitine (PLC) regulates the amount of intracellular calcium and reduces penile fibrosis by controlling collagen production and fibroblast proliferation in endothelial cells (8, 18). In a study conducted by Cavallini and Biagiotti in 2001 involving 48 Peyronie's patients, patients were treated with 20 mg of tamoxifen and were given twice a day for three months. Acetyl-L-carnitine was found to be more effective than tamoxifen in reducing curvature and pain and preventing disease progression. Both drugs were found to be equally effective in reducing the amount of penile plaque size (19). In a study conducted by the same group in 2002, the combination of intralesional Verapamil (10mg per week for ten months) and PLC (2g/day for three months) was combined with tamoxifen reported to give better results compared.

#### 5. Q-10

##### Mechanism

Q10; It is a lipophilic, organic, vitamin-like, and potent antioxidant found in the body (1, 20, 21). It has a role

in protecting cells against ischemia, oxidative stress, and oxidative damage by polyunsaturated fatty acids. People with Peyronie's disease have inflammation and overexpression of the TGF pathway in their fibroblasts. Q10 activates Nrf2, which increases antioxidant proteins that protect against oxidative damage activated by inflammation. Nrf2 suppresses the expression of TGF-21. In addition, the increase in oxidative stress damages the tissue, and it has been said that Nrf2 can indirectly initiate cell division for this injury (21).

##### Evidence

Overexpression of Nrf2 in experiments with Q10, mouse liver, and embryonic fibroblast cells; Expressions of alpha-smooth muscle actin and TGF-21 were suppressed (21). In a prospective, double-blind, placebo-controlled randomized study, an improvement in curvature was observed in 54.3% of patients and a 40% reduction in plaque size; these rates were lower in the placebo group. The increase in curvature was 14.8% in Q10 and 69.5% in placebo. In erectile function, it was 51.9% versus 8.6% in placebo. As a result, in studies conducted; Since there is a decrease in penile curvature and plaque size and improvement in erectile function, it can be said that Q10 has a protective effect on the course of the disease (22).

#### 6. Potassium Para-amino Benzoate (POTABA)

##### Mechanism

POTABA, first used for Peyronie's disease in 1959, is an anti-inflammatory and antifibrotic drug that inhibits abnormal fibroblast growth and secretion of extracellular fluid components (1, 5, 23). POTABA; It reduces fibrogenesis by increasing the oxygen uptake of the tissue and supporting the activity of monoamine oxidase, which enables the breakdown of serotonin (24).

##### Evidence

In a double-blind, placebo-controlled study, POTABA showed a 74.3% reduction in plaque size compared to placebo, but no difference was found in curvature and pain (22, 24). Researchers said that POTABA prevented and stabilized the degree of curvature (22, 25). It is not commonly used because it has itching, anxiety, chills, cold sweats, confusion, difficulty in concentration, and severe gastrointestinal side effects and is expensive (24, 26). It has also been reported in a study that it may cause hepatitis (27). It is taken in 4 doses of 3 grams per day, and Its use is also limited due to the high daily dose (22). For these reasons, data on the efficacy of POTABA are scarce (28).

## 7. Oral Treatment Methods Summary

Studies have shown that colchicine and POTABA have some severe side effects. Evidence on the effectiveness of oral treatments is insufficient, and there are few RCT studies (23, 29). In the guideline published by the EAU in 2019, it is recommended that vitamin E should not be used in patients who want to significantly reduce the curvature. According to the International Consultation on Sexual Medicine 2016 guideline (ICSM), oral treatments have been reported to be minimally beneficial or not beneficial in reducing the clinical features of Peyronie's disease; therefore, their use is not recommended (30, 31).

## TOPICAL THERAPY METHODS

### 1. Verapamil

#### Mechanism

Verapamil is used as a calcium channel blocker in the treatment of Peyronie's disease. In this way, it is aimed to increase collagenase activity and to prevent the secretion of extracellular fluid proteins (32).

#### Evidence

Studies are continuing on the use of Verapamil, which is also used intralesional, as a topical treatment method. There are data in some studies that Verapamil does not reach the tunica albuginea (33), but dexamethasone and Verapamil applied by iontophoresis have been shown to reduce the curvature, especially in patients with a curvature degree of less than (30, 34).

At the same time, a guideline published by the EAU in 2019 stated that topical Verapamil reduces penile curvature and plaque size (35).

### 2. H-100 Gel

#### Mechanism

H-100, topically applied for the non-surgical treatment of Peyronie's disease, it is a gel with the chemical content of Nicardipine, superoxide dismutase, and emu oil. Emu oil, rich in fatty acids, has been used as a transdermal carrier agent (36). Superoxide dismutase provides clearance of free oxygen radicals that play a role in inflammation (37). Nicardipine is a calcium channel blocker. It may also be effective in reducing glycosaminoglycan synthesis and blocking collagen production (38).

#### Evidence

In a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of H-100, 22 patients with acute-phase Peyronie's disease were examined. During the first three months, half of the patients received H-100, and the other half received a placebo. For the next three months, all patients received H-100. An increase in penile length (22.6%), a decrease in curvature (40.8%), and a decrease in pain level (85.7%) were observed in patients who received H-100 for six months. An increase in penile length (6.8%) was observed in patients who received a placebo for the first three months, but no improvement was observed in other parameters. Patients who started taking H-100 after taking a placebo had an increase in penile length (17.5%), a decrease in curvature (37.1%), and a decrease in pain level (40%). The treatment had side effects in only three patients, which was self-limiting skin rash. Although this study yielded positive results, due to the small size of the study, more data on H-100 are needed before routine use (39).

### 3. Liposomal Recombinant Human Superoxide Dismutase (Liposomal RHSD)

#### Mechanism

In the treatment of liposomal RHSD, a topical gel containing superoxide dismutase is applied to the patient. Theoretically, the aim is to stop the inflammatory steps as a result of superoxide dismutase breaking down free oxygen radicals and throwing them out of the body, and thus slowing down and limiting the progression of the disease.

#### Evidence

In placebo, controlled randomized clinical trials, 39 patients suffering from bothersome pain from Peyronie's disease were treated with liposomal RHSD and placebo, and when observed for 4-week periods, significant pain reduction was observed after 28 days compared to placebo. At the end of 56 days, 89% of the patients who were treated with liposomal RHSD had a significant reduction in their pain. Recovery in other symptoms of the disease occurred on the 84th day. Plaque consistency decreased in 38% of patients, plaque size decreased by 47%, and improved penile curvature by 5-30 degrees in 23% of patients. Liposomal RHSD treatment also reduced the rate of disease progression, which rose to 40%, to less than 10%. In conclusion, while liposomal RHSD treatment in Peyronie's disease reduced pain, it also showed improvements in other symptoms (40).

#### 4. Transdermal Electromotive Drug Administration (EMDA)

In this method, also known as iontophoresis, the aim is to deliver the drug to be applied to the tunica albuginea tissue in the targeted area. Transdermal transfer of the therapeutic agent is achieved by electrokinetic transport of charged molecules (41). There are also studies indicating that this method is more effective in reducing erectile pain than intralesional applied dexamethasone and Verapamil (42).

#### 5. Topical Treatment Methods Summary

Research continues on the adequacy of topical treatment methods. Although there are studies showing that it can be effective in reducing curvature and pain, there is no topical treatment method approved by the FDA yet. Although there are studies showing that topical Verapamil and EMDA may work, as stated in the EAU guidelines, there is no data to provide a definitive solution.

### TRACTION AND VACUUM TREATMENTS

#### 1. Penile Traction Therapy

##### Mechanism

This treatment is performed using the penile traction device (PTD). The PTT works by holding the penis in the cradle and subjecting it to gentle and gradual traction forces that can be achieved by adding dynamic rods and small metal extensions to the cradle frame every few weeks (43).

##### Evidence

In *in vitro* studies, it has been determined that the secretion of matrix metalloproteinase-8 (MMP-8), which has an effect on collagen degradation, increases significantly while it is under the effect of traction in penile plaque tunica albuginea cells. PTT plays a role in the rearrangement of these collagen fibrils and in reducing the activity of myofibroblast cells.

In men with early-stage Peyronie's disease, when the traction device was used for at least 4 hours a day for a total of 3-6 months, an increase in mean penile length and a 14° decrease in mean erect penile curvature were observed (44). When PTT was applied to Peyronie's patients in a stable period for an average of five hours per day for six months, approximately 17 degrees (33%) improvement in penile curvature was observed. An

increase in erect penis circumference and flaccid penile length has been observed (45). In men with at least 12 months of Peyronie's disease and pre-existing curvature below 50°, penile curvature decreased from 31° to 27° on average as a result of using the traction device for 5-9 hours a day has fallen. As a result, no significant improvement in penile curvature was observed (46). In acute phase Peyronie's patients, a decrease of approximately 20 degrees in penile curvature, a significant increase in erectile function, and a significant improvement in penile pain were observed when PTT was applied between 6-9 hours daily for a minimum of 6 months. In 40% of the patients, the need for surgery disappeared (47).

In a randomized controlled study using a new device called "Penimaster PRO" in men with stable Peyronie's disease and a minimum of 45 degrees penile curvature, after 3-8 hours of PTT per day for 12 weeks, an improvement of approximately 31 degrees was observed in penile curvature and the daily application time was increased (48).

In men with stable Peyronie's disease and a minimum of 30 degrees penile curvature, "RestoreX" a new traction device, was applied daily for 30-90 minutes for three months, and a decrease of approximately 12 degrees in penile curvature and an average increase of 1.5 cm in penile length were observed (49).

#### 2. Vacuum Erection Device (VED)

##### Mechanism

VED treatment is performed with devices that create negative pressure to induce events such as retrograde venous blood flow, enlargement of the cavernous sinuses, and increased arterial blood flow.

##### Evidence

As a result of the use of VED 2 times a day (10 minutes), reduction in penile pain, approximately 0.5 cm elongation in erect penis length, and 5-25 degree decrease in curvature were observed (50).

An average of 16 degrees improvement in penile curvature was seen in men who used VEDs for 10-minute periods twice a day for 11 months. In addition, it was understood that the improvement was not related to the patient's age and that the treatment gave better results in patients with a high degree of curvature (51).



### 3. Traction and Vacuum Therapies Summary:

In recent years, VED and PTT have received great attention as a new non-surgical treatment option for Peyronie's disease. These seemingly safe and well-tolerated non-surgical treatments require a great deal of patient compliance and commitment. Current literature suggests that selected cases may benefit from a conservative approach with PTT and VED, resulting in a reduction in penile deformity.

Evidence for PTT is limited. However, while some studies did not show significant improvement, several studies have shown a potential benefit of PTT when used as monotherapy or in combination with oral medications, intralesional injections, or surgery, with significant improvement in curvature reduction, erectile function, and penile pain. In addition, PTT was found to be more effective in acute phase Peyronie's patients, and some patients did not require surgery. Future studies will identify key points, including issues of patient compliance and duration of use. Although there are not many studies on VED treatment, a significant improvement was observed in Peyronie's patients, and some patients did not require surgical intervention. More studies on this treatment are needed.

## SHOCK WAVE THERAPY

### 1. Extracorporeal Shock Therapy (ESWT)

#### Mechanism

Although the mechanism of action of ESWT has not yet been clearly revealed, it is a form of treatment that aims at the effect of acoustic pressure waves sent from the outside to the body, defines the energy size per mm<sup>2</sup>, and its density is measured in mJ/mm<sup>2</sup>.

#### Evidence

ESWT was first described in 1989 by Bellorofonte C et al. Although it was applied to patients with cavernous fibrosis due to Peyronie's disease, it was applied by Butz and Teichert in 1996 considering that it would be a well-tolerated method. In the study, 52 patients were used and followed up for nine months. 83% reduction in pain, 40% improvement in curvatures, and 48% improvement in sexual functions were observed. If we look at the recent studies that measured the effectiveness of ESWT in Peyronie's disease; We consider one as randomized without placebo/sham group, three as RCT, and the rest as observational studies. In the studies, treatment methods were applied once a week for 4-6 weeks with an energy

density of 0.25-0.29 mJ/mm<sup>2</sup> and the number of pulses varying between 2000-3000. Attention was paid to the fact that the patients included in the study were stable for more than six months without any previous treatment, and at least three months old who received oral treatment before and failed. Hatzichristodoulou et al. (52), while statistically similar percentages were found between the change of curvature and plaque size in the active treatment group and the sham group in the RCT, it was observed that the ESWT treatment group showed greater improvement in the mean pain over VAS than the placebo/sham group. In addition, in this study, 85% reduction in pain was observed in the ESWT group, while the pain reduction was 48% in the placebo/sham group. In 2009 Palmieri et al. (53) study, 100 patients with Peyronie's disease under 12 months were divided into control group and ESWT. The age range was 18-75 years, and the patients were followed for 12-24 weeks in terms of painful erection, plaque size, erectile function, penile curvature, and quality of life. There was an insignificant reduction in curvature and plaque size in the ESWT group, while a small increase was found in the placebo/sham group. In this study, the mean pain over VAS was also looked at, and it was observed that ESWT from the two groups provided more improvement than the placebo/sham group. In 2004, Hauck et al. in the meta-analysis of; It has been stated that the success in ESWT is in very wide ranges such as 0-74% for penile curvature, 0-58% for plaque size, 12-75% for sexual function and 56-100% for penile pain. In the meta-analysis; It was stated that ESWT treatment did not statistically change the degree of curvature, plaque size, and erection score; only after treatment it reduced pain from 37% to 9%, and ESWT application statistically reduced penile pain (54).

### 2. Shock Wave Therapy Summary

ESWT is a treatment based on sending shock waves from outside to the body. ESWT experiments showed that the degree of curvature, plaque size, and pain decreased, while the erection score increased when first performed. However, in the experiments conducted in the following years, the degree of curvature does not significantly change plaque size, erection score but significantly reduces pain.

## PLAQUE INJECTION TREATMENTS

### 1. Interferon-Alfa-2B

#### Mechanism

Interferons are low molecular weight proteins and glycoproteins responsible for immunoregulation that can

be synthesized endogenously in the human body. In vitro studies have shown that interferon-alpha 2b (INF- $\alpha$ -2b) suppresses fibroblast proliferation with its antifibrotic effect, decreases collagen and extracellular matrix production in fibroblast cells, and increases collagenase production (51)

### Evidence

In the first study, plaque softening, 50% reduction in curvature, and total pain relief were reported. A 1x10<sup>6</sup>-unit dose of INF- $\alpha$ -2b was injected subcutaneously into the plates in a later study. Post-injection pain relief has been reported, with a reduction in 28% of non-calcified or minimally calcified plaques size. Following this treatment, the amount of the drug was increased (3x10<sup>6</sup> unit dose INF- $\alpha$ -2b), and the same treatment was applied, resulting in no reduction in plaque and 82% of side effects were observed. In another study, pain relief, reduction in penile curvature, plaque softening, and reduction in plaque size were reported in patients who received intralesional saline as control and 1.5 x 10<sup>6</sup> units of INF- $\alpha$ -2b injection as a treatment (55).

In the most scientifically finalized study of the efficacy of intralesional INF- $\alpha$ -2b in Peyronie's disease, 5x10<sup>6</sup> INF- $\alpha$ -2b was administered to patients. Penile curvature, plaque characteristics (size, density), penile pain, erectile function, and penile hemodynamic parameters were evaluated in the study. At the end of this study, mean penile curvature decreased from 49.9 degrees to 36.4 degrees, mean plaque size reduced by 4.8 cm to 2.2, mean plaque density decreased from 2.07 to 1.84, pain resolution was 67.7% of patients a decrease in of them, and an increase in penile blood flow was observed. However, no difference in mean erectile function was observed. These results provide the best evidence of efficacy to support the use of intralesional interferon in patients.

Taking an overdose of INF- $\alpha$ -2b has side effects such as flu-like syndrome, anorexia, rashes, hypotension, and cardiac arrhythmia. The use of analgesic drugs before intralesional injection of INF- $\alpha$ -2b reduces these side effects (9).

## 2. Clostridium Collagenase Histolicum (CCh)

### Mechanism

CCh, which is a mixture of AUX-I and AUX-II enzymes produced by Clostridium histolyticum bacteria, both reduces the abnormal expression of type 1 and 3 collagens by enzymatically disrupting the triple helix structure in

pathological collagen plaques in Peyronie's disease and destroys these plaques that cause PD curvature.

This enzyme does not act on arteries, nerves, and surrounding connective tissues containing collagen type 4. 54 The efficacy of collagenase treatment on plaque tissue was discovered in 2013 with the phase 3 IMPRESS trial and in vitro studies (56). As a result, CCh, which has demonstrated efficacy and safety in clinical trials for the conservative treatment of Peyronie's disease, has become the only FDA-approved treatment (57).

### Evidence

A double-blind, randomized, placebo-controlled study involving 418 patients was completed in 4 treatment cycles of 2 injections 24-72 hours apart. Curvature, erectile function improved, pain, and plaque size decreased (58). In a retrospective cohort study of 918 patients treated between April 2014 and March 2018 and collected from 5 different institutions, penile curvature decreased from an average of 48.2 degrees before treatment to 32.9 degrees after treatment, and it was determined that there was an improvement of 30.1% compared to the baseline. 68.7% of patients had 20% or more improvement in penile curvature. In 502 patients who completed four or more cycles of treatment, penile curvature decreased from an average of 49.7 degrees to 32.7 degrees and showed a 33% improvement from baseline. Of these patients, 74.4% experienced 20% or greater improvement in curvature. Treatment complications developed in 9% of the patients. The number of CCh cycles received was a predictor of curvature improvement. This multi-institutional meta-analysis confirms the safety and efficacy of CCh therapy in men with Peyronie's disease (59). Improvements in penile curvature and Peyronie's Disease Questionnaire score continued without additional CCh therapy up to 5 years after intralesional CCh therapy, and no problems were identified (60)

Most adverse events associated with intralesional CCh therapy (hematoma, bruising, pain, and swelling in the penis) were mild or moderate and resolved without intervention. In addition, the use of CCh was not associated with penile shortening (61). In the sexual function questionnaire, in which a total of 24 couples participated, the satisfaction of the patient and the female sexual partner with the treatment was 67% and 71%, respectively. As a result, CCh treatment provides a significant benefit to a couple's sexual health. Treatment is associated with increased partner satisfaction and increased ability to have sexual intercourse (62, 63).

### 3. Verapamil

#### Mechanism

Verapamil, a calcium channel blocker, was first described in 1994 by Levine et al. it has been shown that it can be used in Peyronie's treatment because it changes the metabolism of fibroblasts, inhibits calcium-dependent extracellular collagen transport, and increases collagenase activity (64).

#### Evidence

In a meta-analysis of seven different studies, intralesional injection of Verapamil significantly improved sexual function ( $p < 0.0005$ ) and penile curvature ( $p < 0.005$ ) in patients. There is an imprecise but significant reduction in pain after the treatment, but less effect on plaque size ( $p > .05$ ) (65). In a prospective, single-blind, randomized study, the use of Verapamil in Peyronie's disease showed improvement in penile curvature and reduction in plaque size (66).

Verapamil injection is clinically safe for patients with Peyronie's disease and appears to cause a rapid and beneficial effect in patients for reducing plaque size. Intralesional injection of Verapamil for Peyronie's disease can reduce pain, reduce penile curvature, and improve sexual function (32).

### 4. Nicardipine

#### Mechanism

Following the success of Verapamil used in the treatment of Peyronie's disease, universities began to conduct randomized placebo-controlled studies on the potency of Nicardipine—a dihydropyridine based on this treatment (calcium channel blocker). Compared with Verapamil, the possibility of its high efficacy in reducing extracellular substance synthesis between the acute and chronic phases of Peyronie's disease was considered.

#### Evidence

The study included 74 randomly selected men. Patients are given Nicardipine (10 mg in 10 ml of distilled water) or 10 ml of normal saline every two weeks for ten weeks (6 doses in total). The clinical outcomes evaluated were pain during erection, plaque size, erectile function (according to the international index of erectile function 5 [IIEF-5]), and penile curvature.

While the pain was more pronounced in the nicardipine group, it decreased in both groups ( $p: 0.019$ ). At 48 weeks,

significant improvements in mean IIEF-5 score and plaque size were noted in the nicardipine group only ( $p < 0.0001$  and  $p: 0.0004$ , respectively). Penile slope improved significantly and to a similar extent in both groups at the end of the study, consistent with previous Verapamil studies (67, 68).

### 5. Intraplaque Injection Therapy Summary

As a result of studies with intralesional IFN- $\alpha$ -2b, it is suitable for use in treatment, as the use of the right amount shows a significant improvement in patients. Intralesional CCh and intralesional verapamil treatment can be used clinically in Peyronie's disease as it improves curvature, erectile function and reduces pain and plaque size. As a result of the study, the authors concluded that Nicardipine is an alternative and effective option for patients with transitional phase Peyronie's disease. Nevertheless, it is thought that the search for a non-surgical treatment for Peyronie's disease should continue.

## EXPERIMENTAL TREATMENTS

### 1. Stem Cell Therapy

#### Mechanism

Adipose tissue-derived regenerative cell (ADSC or SVF) treatment is based on enzymatic reactions of approximately 50 cc of fat taken from the sides of the penis. This fluid, which decreases as a result of enzymatic reactions, is injected into the body from the right and left sides of the penis. In Peyronie's disease, we inject it into the plaque in the penis. However, injecting this liquid alone is not enough. At least six sessions of shock wave therapy should also follow this process because shock wave therapy stimulates stem cells and activates them.

Of course, this treatment is not only used in Peyronie's patients. It is also generally used in patients with erectile dysfunction.

#### Evidence

In animal experiments, TGF- $\beta$ 1 was given to rats treated with ADSC. After this situation, it was noticed that the development of Peyronie's disease was prevented. In addition, it was determined that elastic tissue and type 3 collagen tissue decreased.<sup>68</sup> In an article published in 2016, a table was given as a result of the application of ADSC and shock wave together. According to this table, the penile hardness of 7 of 11 participants increased. One of the remaining four people already had a normal erection.



The other 3 had an erection that would allow them to have sexual intercourse, although it was not normal. In total, the degree of hardening score increased from 2.7 to 3.5 on average (69).

## 2. Experimental Treatments Summary

Stem cell therapy is known as a complicated and new treatment method that is applied with the support of liquid injection and then shock wave therapy. In experiments, it was noted that it prevented the development of Peyronie's disease and reduced the production of type 3 collagen. It has been found to increase the degree of hardening.

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