

# Peyronie's disease: clinical treatment

## Participants:

Giuliano Aita<sup>1</sup>

Carlos Teodósio da Ros<sup>1</sup>

Antonio Silvinato<sup>1</sup>

 Wanderley Marques Bernardo<sup>2</sup>

Created on: February 18, 2018

1. Sociedade Brasileira de Urologia, Rio de Janeiro, RJ, Brasil
  2. Coordenador do Programa Diretrizes da Associação Médica Brasileira, São Paulo, SP, Brasil
- \* This guideline replaces the previous 2016 version.

<http://dx.doi.org/10.1590/1806-9282.65.10.1231>

*The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize producers to assist the reasoning and decision-making of doctors.*

*The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.*

Peyronie's disease is an acquired disorder of the connective tissue gained, attributed to repetitive microvascular injury or trauma during sexual intercourse, which leads to the appearance of fibrous plaques or nodules in the tunica albuginea of the penis, reducing local elasticity and curving the penis during an erection. The purpose of this guideline is to provide recommendations that may assist in the decision-making process regarding the clinical treatment for patients with a diagnosis of Peyronie's disease (PD). For this, a systematic review of the literature, was performed, without period restriction, in the MEDLINE database, retrieving 759 papers, of which 37 were selected to respond to clinical doubt. The details about the methodology and the results are set out in Appendix I.

## INTRODUCTION

The etiopathogenesis of Peyronie's Disease (PD) is not fully known, but there is a possibility of immuno-

logic genesis<sup>1</sup>(D). It is an acquired disorder of the connective tissue gained, attributed to repetitive microvascular injury or trauma during sexual intercourse, which leads to the appearance of fibrous plaques or nodules in the tunica albuginea of the penis, reducing local elasticity and curving the penis during erection<sup>1,2</sup>(D). In adults, it is often associated with Dupuytren's contracture (thickening of the palm of the hand that consequently modifies the curvature of the fingers)<sup>3</sup>(B), which is not seen in adolescents with PD<sup>4</sup>(B).

The diagnosis is based on the medical and sexual history with penile deformity and pain, difficulty during coitus and erectile dysfunction (ED)<sup>2</sup>(D). The physical examination includes palpation of the nodules (possible in 70% of cases) and the observation of the curvature of the penis during a natural or induced erection<sup>1</sup>(D) or photographs. The penile deformity is the first symptom of the disease in 52% of cases and is present in 94% of affected men<sup>5</sup>(D).

The natural history of the PD can vary from spon-

taneous resolution to progressive worsening of the deformity and ED<sup>1</sup>(D). The treatment can be clinical or surgical<sup>4</sup>(D).

The clinical treatment uses medication via the oral route, intralesional injections, and shockwave therapy<sup>6</sup>(D).

Two stages are observed: the acute phase (first six months, characterized by pain and changes in size and/or number of palpable plates and penile deformity), and the chronic or stable phase (between six and 18 months, with possible disappearance of the pain and the stabilization of the size and number of plates)<sup>7</sup>(D).

The absence of knowledge on this disease contributes to the diagnostic difficulty, which leads to an estimated prevalence lower than the reality. There is also a greater belief in spontaneous cure more than what actually occurs, and the possibility of the disease existing before the age of 40 years is often ignored; with no investigation of the association of PD in cases of ED and no effective clinical and surgical treatment <sup>8</sup>(D).

## RESULTS

### Oral therapy

Non-steroidal oral anti-inflammatory drugs can be administered to patients with active Peyronie's Disease, which requires treatment for pain<sup>9</sup>(D).

Treatment alternatives that use carnitine and tamoxifen<sup>9</sup>(B)<sup>10</sup>(A) have been abandoned, in addition to para-aminobenzoate potassium (Potaba)<sup>11,12</sup>(A), since they have not been associated with significant improvement of pain, curvature, or plaque size.

#### Vitamin E

Randomized controlled trials (RCTs) that evaluated the use of vitamin E alone or combined with other therapies (intralesional interferon [IFN]  $\alpha 2\beta$  or propionyl-L-carnitine) showed no improvement in penile curvature, plaque size, IIEF scores (International Index of Erectile Function) or sexual satisfaction<sup>13,14</sup>(A). However, another RCT showed that vitamin E combined with intralesional verapamil (VII) and antioxidants improved the curvature of the penis, plaque size, and IIEF scores<sup>15</sup>(B).

A prospective cohort study included 58 men with acute PD (beginning <6 months, without ED and who were treated with vitamin E 800 mg/day orally (OR), and colchicine 1 mg/day OR, for six months. Thir-

ty-six patients were smokers and 22 nonsmokers. With a mean follow-up of 10.3 months, there was a reduction among nonsmokers, in comparison with smokers, for curvature (38% versus 54% [ $p < 0.05$ ], respectively) and plaque size (36% vs. 50% [ $p < 0.05$ ], respectively). There was no significant difference in response to pain between the two groups<sup>16</sup>(B).

It should be noted that vitamin E, in high doses, may increase the risk of cerebrovascular events<sup>17</sup>(A).

### Intralesional therapy

#### Collagenase clostridium

Collagenase clostridium histolyticum (CCH) is comprised of a heterogeneous group of seven different enzymes that have shown remarkable specificity for digesting specific proteins, inside the fibers of collagen type I and type III, in physiological conditions.

Two RCTs, Impress ((Investigation for Maximal Peyronie's Reduction Efficacy and Safety Studies) I and II evaluated results of intralesional infiltration with CCH (0.58 mg) in 417 and 415 patients with PD (penile curvature  $\geq 30$  degrees), respectively, with a maximum of four cycles of treatment, compared with a placebo in a one-year follow-up. Each cycle consisted of two infiltrations with an interval of 24-72 hours, weeks apart. All patients underwent modeling (manipulation of the penis in the contralateral direction of the curvature), which was performed by a urologist after each cycle of treatment. The patients were also instructed to perform the modeling at home, three times a day, between the treatment cycles, and try to straighten the penis, during spontaneous erections, once per day. A post-hoc meta-analysis of these two studies (n=832), analyzing data from 74% of this population, showed that CCH, in comparison with the placebo, improved penile curvature (17 degrees versus 9.3 degrees;  $p < 0.0001$ ); increased the global response reported by the patient (60.8% versus 29.5%;  $p < 0.0001$ ; NNT=4) and increased the risk of adverse events (84.25 versus 36.3%; NNH=2). CCH is associated with improvement in the score of PD symptoms ( $-2.8 \pm 3.8$  versus  $-1.8 \pm 3.5$ ,  $p = 0.0037$ ). The most common adverse events with the use of the CCH were: ecchymosis, swelling, and penile pain. There were six cases of serious adverse events (2.1%) related to treatment with CCH (three cases of corpora rupture and three cases of penile hematoma). No systemic immunological events were reported<sup>18</sup>(A).

The effectiveness of the CCH in comparison with the placebo was also assessed, in a 52-week fol-

low-up, for subgroups (curvature of the penis, duration of disease, calcification, and erectile function) of participants of the Impress I/II studies, maintaining consistent results<sup>19(A)</sup>.

In a before and after study, the safety of intralesional infiltration with CCH in the treatment of PD was evaluated, using a pooled analysis of individual patient data from six studies (n=1,044 men), who received at least one dose of CCH (average number of 7.2 infiltrations/patient). Adverse events (AE) related to treatment ( $\geq 1$  event) occurred in 85.8% of the 1,044 patients, and most were of mild/moderate severity. The more common AE were: penile hematoma in 50.2%, penile pain in 33.5%, swelling in 28.9%, and pain at the injection site in 24.1%. A total of 0.9% severe adverse events were reported related to treatment, including hematoma in 0.5% and corpora rupture in 0.4%<sup>20(B)</sup>. These studies did not evaluate the use of collagenase in patients with hourglass deformity or ventral curvature, with calcified plaque or plaque located on the penis base.

The efficacy and safety of CHD in the treatment of PD in the acute phase were evaluated in a historical cohort study. The acute phase was considered the presence of pain and penile plaque, for no more than 12 months. The outcomes evaluated were the change in curvature after CCH treatment, regardless of the number of CCH cycles received, and the frequency of adverse events related to the treatment, comparing a group of patients in the acute phase and another in the chronic phase of PD. A total of 162 patients were included in the study, of whom 36 (22%) were classified as in the acute phase of PD (group 1) and the remaining 126 (78%) as in the stable phase (group 2). There was no significant difference in the change of curvature between the acute and stable group (16.7 versus 15.6 degrees, respectively;  $p=0.654$ ). There was also no difference in the frequency of adverse events related to the treatment between the acute phase group (four patients, 11%) and the stable phase group (12 patients, 10%,  $p=0.778$ ). Therefore, the use of CCH in the acute phase of DP is effective and safe<sup>21(B)</sup>.

### Interferon $\alpha$ -2 $\beta$

A multicenter RCT (reported by Hellström et al.<sup>22</sup> and Kendirci et al.<sup>23</sup>) evaluated intralesional interferon (INF)  $\alpha$ -2b and included patients who presented symptoms of PD for more than 12 months and curvature of at least 30 degrees (n=117). The intervention

group received intralesional INF  $\alpha$ -2 $\beta$  5 x 10<sup>6</sup> units twice a week for 12 weeks and was compared with a placebo (saline solution). INF  $\alpha$ -2b, compared with the placebo, in a three-month follow-up, decreased, on average, the curvature (13 degrees versus 4 degrees;  $p<0.01$ ); reduced, on average, the size of the plaque (54.6% versus 19.8%;  $p<0.001$ ), and increased the number of patients with resolution of pain in during erection (67% versus 28%, NNT=3). Penile duplex Doppler ultrasonography showed significant improvements in peak systolic velocity and mean resistive index in the intralesional INF  $\alpha$ -2 $\beta$  group, but not in the placebo group. The adverse events of intralesional INF  $\alpha$ -2 $\beta$  treatment included penile edema, inflammation, ecchymosis, and flu-like symptoms (fever and arthralgia), which responded well to NSAIDs<sup>22,23(A)</sup>.

Another RCT compared vitamin E 400 IU twice a day for 24 weeks, intralesional interferon  $\alpha$ -2b 5.0 x 10<sup>6</sup> U per week for 12 weeks, and interferon 5 MU per week (for 12 weeks) + Vitamin E 400 IU twice a day (for 24 weeks), in patients with PD in initial stage (average duration of 10.8 months [6 - 18 months]), with at least six months of duration, who presented associated pain, deformity, or penile curvature. Patients with a calcified plaque were excluded from this study. In a six-month follow-up (without losses), there were no statistically significant changes in the objective parameters (degree of penile curvature and plaque size), in comparison with the initial findings in the individual groups or between them ( $p>0.05$  for all comparisons). There was no formation of new plaques or calcification during the study. All patients treated with NPI  $\alpha$ -2b had flu-like symptoms (fever, myalgia, and arthralgia)<sup>14</sup>.

The effectiveness of intralesional INF- $\alpha$ 2b for the PD was evaluated in a before and after retrospective study, reviewing the impact of the moment of therapy from its beginning and the possible predictive variables of the response. A total of 127 patients with pre-treatment curvature (mean  $\pm$  SD) of 42.4  $\pm$  18.6 degrees received 12 injections (median), fortnightly, of INF- $\alpha$ 2B. The PD time of evolution was 2.0 years (median)<sup>24(C)</sup>.

The response was defined as an improvement of 20% or more in the curvature. Out of the total number of patients, 54% responded to therapy with an improvement in the global mean by 9.0 degrees ( $p<0.001$ ). Patients with curvature  $>30$  degrees had a higher probability of response (86% response,

$p < 0.001$ ); however, an improvement in the pre-treatment curvature was observed in all cases. There was no improvement in the vascular condition of the penis or in ultrasound parameters. Age, pre-treatment curvature, vascular state, ultrasound findings, site of curvature, and IIEF score did not predict the response to therapy. The duration of Peyronie's Disease did not affect the changes in curvature<sup>24</sup>(C).

A retrospective cohort compared the results of treatment for PD in men undergoing intralesional INF- $\alpha$ 2b, with plaques on different sites. It included 131 patients who received (median) 12 injections (6-24) of intralesional INF- $\alpha$ 2b. The patients were stratified in cohorts of ventral plaques (curvature of  $44.5 \pm 21.5$  degrees) and dorsal/side ( $42.5 \pm 18.6$  degrees) with a positive response defined as a reduction of the curvature by 20% or more. In total, 91% of the patients responded to the therapy. No significant differences were observed between the two groups in relation to the response rates (54% versus 52%,  $p = 0.92$ ) or absolute changes in curvature ( $8.7 \pm 12.6$  degrees versus  $9.3 \pm 17.7$  degrees,  $p = 0.84$ ). Therefore, there is improvement with intralesional INF- $\alpha$ 2b therapy in PD patients, regardless of the site of plaques<sup>25</sup>(B).

### Verapamil

A placebo-controlled RCT compared intralesional (IL) verapamil with IL saline solution (weekly injections for six months), in patients with PD for an average duration of 16 months (11-24 months) and a volume of plaques, on average, of 1.4 ccs (range of 1.5 to 2.7 cc) before therapy. In comparison with a placebo, IL verapamil (dose ranged from 10 to 27 mg) reduced the size of plaques (57% versus 28%, respectively,  $p < 0.04$ ) and improved the quality of erection (43% versus 0%, respectively,  $p < 0.02$ ). There was no difference in the improvement of the curvature between the two groups ( $p > 0.05$ ). As an adverse event, there was ecchymosis at the injection site<sup>26</sup>(B).

Another RCT included 80 patients with PD (without plaque calcification) who were randomized into IL verapamil 10 mg diluted in 10 ml of distilled water (onset of the disease  $20.60 \pm 4.2$  months) versus saline injection (onset of the disease  $22.00 \pm 4.8$  months), two times a week for 12 weeks. In a 24-week follow-up to, there was no difference between the groups in the reduction of the size of the plaque, in pain reduction, reduction of curvature, and improvement of erectile function ( $p > 0.05$  for all comparisons)<sup>27</sup>(B).

In a before and after study, the administration of IL verapamil in 156 patients with PD resulted in an objective decreased of the curvature in 60% of patients (mean of 30 degrees, ranging from 5 to 90 degrees) and improvement in sexual function in 71% of patients, with an average follow-up of 30.4 months<sup>28</sup>(C).

The efficacy of IL verapamil (V) in comparison with intralesional hyaluronic acid (HA) in PD patients ( $n = 140$ ) in the initial phase of the disease (disease duration  $< 12$  months associated with a soft nodule or plaque and/or painful erection and/or recent change in penile curvature) was evaluated in a double-blind, multicenter RCT with 12 weeks of follow-up. One group received intralesional treatment with verapamil (10 mg in 5 mL of NaCl 0.9%) per week for 12 weeks ( $n = 70$ ), while the other received intralesional treatment with HA (sodium hyaluronate [sodium salt of hyaluronic acid] 0.8% highly purified, 16 mg/2 mL) weekly for 12 weeks ( $n = 70$ ). The difference between the size of the plaque post and pre-treatment was  $-1.36$  mm ( $SD \pm 1.27$ ) for the IL V group and  $-1.80$  mm ( $SD \pm 2.47$ ) for the IL HA group ( $p =$  not significant [NS] between the groups). There was no difference in penile curvature in the IL verapamil group, while at the IL AH group the curvature of the penis decreased from 4.60 degrees ( $SD \pm 5.66$ ) from the baseline ( $p < 0.001$ ) and from IL V ( $p < 0.001$ ). Erectile function improved (IIFE-5) in both groups, but without any difference between them ( $p =$  NS). There was a global improvement reported by patients (Patient Global Impression of Improvement [PGI-I]), which was greater in the IL AH group (4.0 versus 2.0;  $p < 0.05$ ). No adverse events were reported. Therefore, IL HA showed greater efficacy in terms of penile curvature and global improvement, reported by the patient, in comparison with the IL verapamil<sup>29</sup>(A).

### Topical pharmacological agents

#### 3.1 H-100 Gel

A recent double-blind RCT evaluated the safety and efficacy of the H-100 gel, a combination of nicardipine, superoxide dismutase, and emu oil, applied topically to treat the acute phase of PD, defined as a disease with 12 months duration. Twenty-two patients in the acute phase of PD were randomized to receive H-100 ( $n = 11$ ) or a placebo ( $n = 11$ ) in two daily applications, for three months. After three months, all patients in the study received three months of treatment with H-100. The patients could not use a treatment for PD in the six months prior to the randomization. H-100 showed

significant improvement in all parameters of PD in six months: average increase of the length of the penis taut (22.6%,  $p=0.0002$ ), an average reduction of curvature (40.8%,  $p=0.0014$ ) and an average reduction of the level of pain (85.7%,  $p=0.004$ ). The placebo group showed no significant improvement, except for an average increase in the length of the penis taut (6.8%,  $p=0.009$ ). The patients who crossed over from the placebo to H-100 showed significant improvement in all parameters: average increase of the length of the penis taut (17.5%,  $p=0.000007$ ), an average reduction of curvature (37.1%,  $p=0.006$ ), and an average reduction of the level of pain (40%,  $p=0.17$ ). The drug was well-tolerated, and a cutaneous rash was the only adverse event<sup>30(B)</sup>.

### Iontophoresis with verapamil

A nonblind RCT with a loss of 25% of the population included randomized 96 patients with PD to receive verapamil 5 mg and dexamethasone 8 mg ( $n=47$ ) or lidocaine 2% ( $n=49$ ), by means of transdermal therapy by iontophoresis, in sessions of 20 minutes four times a week for six weeks. The verapamil and dexamethasone group, in comparison with the lidocaine group, had decreased, on average, penile curvature (22 degrees *versus* 0 degrees;  $p<0.0001$ ) and plaque volume (476 mm<sup>3</sup> *versus* 4.8 mm<sup>3</sup>,  $p<0.0001$ ). There was no difference in pain reduction between both groups<sup>31(B)</sup>.

Another double-blind, placebo-controlled RCT evaluated the efficacy of verapamil administered by iontophoresis. A total of 42 men with PD were randomized to receive verapamil 10 mg in 4 cm<sup>3</sup> of saline solution ( $n=23$ ) or 4 cm<sup>3</sup> of saline solution ( $n=19$ ) administered by iontophoresis, twice a week for three months. To better assess the effectiveness, the total number of patients with significant improvement in curvature (20 degrees or more) was calculated and compared. There was no difference in the reduction of penile curvature between the groups (30.4% in the verapamil group and 21.1% in the placebo group; ARI = 9.3%, 95% CI -0.356 to 0.170; NNH=NS)<sup>32(B)</sup>.

### Extracorporeal shockwaves

A systematic review examined the results from three RCTs that evaluated the efficacy of extracorporeal shockwave therapy, but the mechanism of action is not yet understood. The studies included 238 patients. Hatzichristodoulou et al. and Chitale et al. included patients in the stable phase of the disease,

while in the study of Palmiere et al., patients who had symptoms present for a period of fewer than 12 months were eligible. Therefore, the last study may have included patients in the acute phase of PD. The patients in the Hatzichristodoulou et al. study were treated pharmacologically without effect before the inclusion, while the other two studies used ESWT (Extracorporeal Shockwave Therapy) as the first-line treatment. The follow-up ranged between four weeks and six months between the studies. The RCTs showed improvement in pain with extracorporeal shockwaves therapy, but there were no significant reductions in objective measures of the severity of PD (penile curvature and plaque size). Hatzichristodoulou et al. showed that, although the ESWT can improve pain, this is the only symptom of PD that often resolves itself over time, without intervention<sup>33(A)</sup>.

Results of a meta-analysis revealed that ESWT can be an effective and relatively safe choice for PD patients with plaques and painful erection. They included in this meta-analysis six comparative studies (a total of 443 patients). Three studies, including a total of 225 patients, evaluated the size of the plaque. The pooled data from these studies revealed a significant reduction in the size of the plaque in the ESWT group compared with the control group (OR 2.07, 95% CI 1.11-3.85,  $I^2=0\%$ ;  $p=0.02$ ). The data describing the improvement of the penile curvature were grouped (three studies), including 198 men, and showed no difference between the groups (OR 1.88, 95% CI: 0.97-3.65,  $I^2=0\%$ ;  $p=0.06$ ). There was no difference in sexual function between the ESWT and placebo groups (six studies and 296 patients; OR 2.22, CI 95% 0.69-7.11;  $I^2=62\%$ ,  $p=0.18$ )<sup>34(A)</sup>.

This meta-analysis showed that the ESWT group, in comparison with the control group, had more patients with pain relief (three studies and a total of 212 patients; OR 4.46, CI 95% 2.29-8.68,  $I^2=15\%$ ,  $p<0.0001$ ) and a larger number of patients with complete remission of the pain (three studies and 164 patients; OR 5.86, CI 95% 2.66-12.92,  $I^2=56\%$ ;  $p<0.0001$ ), but no improvement of the curvature or sexual function. The results were similar for sensitivity analysis and publication bias when only RCTs were included. In this study, ESWT was well tolerated, in general, although there was an incidence of some complications that do not require intervention, such as penile bruises and urethral bleeding<sup>34(A)</sup>.

ESWT may be considered in men with significant pain due to PD, but they should be informed that it



is unlikely to improve penile curvature and that, in many cases, the pain is resolved over time without intervention.

### Radiotherapy (rt)

A non-randomized clinical trial compared two doses of radiotherapy (one treatment of 2.2 to 5.5 Gy versus two treatments with a total of 4.4 to 10.4 Gy) with an untreated control group. With regard to the effects on the curvature, the rates of improvement were similar in the two RT groups (50% and 39%) and in the untreated control group (52%). Regarding plaques, the rates of improvement in the RT groups (55% and 44%) were equal to those of the untreated control group (58%). The improvement rates for pain were similar in both RT groups (100% and 92.3%) and in the untreated control group (100%)<sup>35</sup>(B).

### Recommendation

- In combined therapy (e.g., IL verapamil and anti-oxidants, colchicine), vitamin E can bring some benefits, but alone, like other oral treatments, it should not be used to improve penile curvature or plaque size. (B)
  - Intralesional collagenase clostridium is effective and safe both in the acute and stable phases of PD. (B)
  - Intralesional injections of collagenase clostridium decreases the curvature and plaques in patients with curvatures >30° and <90°, with minimal severe adverse events. (B)
  - Injections of intralesional interferon  $\alpha 2b$  can improve the curvature, decrease the size of uncalcified plaques, and pain. (B)
  - There is a discrete improvement with intralesional INF- $\alpha 2b$  therapy in PD patients, regardless of the site of plaques. (B).
  - Intralesional injections of verapamil may result in a reduction of penile curvature and plaque size. (B)
  - IL hyaluronic acid showed greater efficacy in terms of penile curvature and global improvement, reported by the patient, in comparison with the IL verapamil. (A)
  - There is controversy regarding the use of iontophoresis with verapamil in the treatment of PD. (B)
    - Extracorporeal shockwaves can improve pain; however, that symptom of PD is often resolved over time, without any intervention. (A)
    - Extracorporeal shockwaves do not improve penile curvature in PD nor the size plaques. (A)
    - Radiotherapy should not be indicated for the treatment of PD.

## ANNEX I

### Clinical question

What are the clinical therapy practices for Peyronie's Disease?

### Eligibility criteria

The main reasons for exclusion were: they did not respond to the PICO and study design.

Narrative reviews, case studies, series of cases, studies with preliminary results presentations were, initially, excluded.

### Search for papers

#### Database

The scientific databases consulted were Medline (via PubMed), Central Cochrane, and references of the selected studies.

#### Identification of descriptors

<b>P</b>	Peyronie's Disease
<b>I</b>	Clinical treatment
<b>C</b>	Another clinical treatment, placebo, or no treatment
<b>O</b>	Benefit or damage

#### Research strategy

Searches conducted until February 12, 2018.

#### Medline via PubMed

#1 (Peyronie's Disease OR Peyronies Disease OR Peyronie Disease OR Penile Induration) AND (Therapy/Broad[filter] OR systematic[sb])

#2 (Peyronie's Disease OR Peyronies Disease OR Peyronie Disease OR Penile Induration) AND (Random\* OR Comparative study OR Comparative studies OR systematic[sb])

#1 OR #2 = 759 studies

#### Central (Cochrane)

(Peyronie's Disease OR Peyronies Disease OR Peyronie Disease OR Penile Induration) = 140

#### Others

Peyronie's Disease = 77

### Critical evaluation

Relevance - clinical importance

This guideline was prepared by means of a clinically relevant question in order to gather information

in medicine to standardize approaches and assist in decision-making.

Reliability - Internal validity

The selection of the studies and the evaluation of the titles and abstracts obtained from the search strategy in the databases consulted were independently and blindly conducted, in total accordance with the inclusion and exclusion criteria. Finally, studies with potential relevance were separated. When the title and the summary were not enlightening, we sought for the full article.

Only studies with texts available in its entirety were considered for critical evaluation.

No restriction was made regarding the year of publication.

Languages: Portuguese, English, and Spanish.

### Results application - External validity

The level of scientific evidence was classified by type of study, according to Oxford<sup>36</sup>(Table 1).

**TABLE 1.** GRADES FOR RECOMMENDATION AND LEVELS OF EVIDENCE

A: Experimental or observational studies of higher consistency.
B: Experimental or observational studies of lower consistency.
C: Uncontrolled case/study reports.
D: Opinion deprived of critical evaluation, based on consensus, physiological studies, or animal models.

The selected evidence was defined as a randomized controlled clinical trial (RCT) and submitted to an appropriate critical evaluation checklist (Table 2). The critical evaluation of RCT allows to classify it according to the Jadad score<sup>37</sup>, considering Jadad trials < three (3) as inconsistent (grade B) and those with score ≥ three (3) consistent (grade A).

When the evidence selected was defined as a comparative study (observational cohorts, or non-randomized clinical trial), it was subjected to an

adequate critical assessment checklist (Table 3), allowing for the classification of the study according to the Newcastle Ottawa Scale<sup>38</sup>, which considered consistent cohort studies with scores ≥ 6, and inconsistent < 6.

**TABLE 2.** PROCESS FOR CRITICAL EVALUATION OF RANDOMIZED CONTROLLED TRIALS

Study data Reference, study design, Jadad, level of evidence	Sample size calculation Estimated differences, power, significance level, total number of patients
Patient selection Inclusion and exclusion criteria	Patients Recruited, randomized, prognostic differences
Randomization Description and blinded allocation	Patient follow-up Time, losses, migration
Treatment protocol Intervention, control, and blinding	Analysis Intention to treat, analyzed intervention and control
Outcomes considered Primary, secondary, measurement instrument for the outcome of interest	Results Benefits or harmful effects in absolute data, benefits or harmful effects on average

A Measurement Tool to Assess Reviews (Amstar)<sup>39</sup> was used to evaluate the quality of the systematic reviews. This tool provides a global quality rating on a scale from 0 to 11, in which 11 represents a review of the highest quality. Quality categories were determined as follows: low (0 to 3 score), medium (4 to 7 score), and high (8 to 11 score). SRs of low and medium quality were excluded.

### Method of extraction and result analysis

For results with available evidence, the population, intervention, outcomes, presence or absence of benefits and/or harmful effects, and controversy will be specifically defined whenever possible.

The results will be presented preferably in absolute data, absolute risk, number needed to treat (NNT) or number needed to harm (NNH) and, eventually, in mean and standard deviation values (Table 4).

**TABLE 3.** PROCESS FOR CRITICAL EVALUATION OF COHORT STUDIES

Representativeness of the exposed and selection of the non-exposed (Max. 2 points)	Exposure definition (Max. 1 point)	Demonstration that the outcome of interest was not present at the beginning of the study (Max. 1 point)	Comparability on the basis of the design or the analysis (Max. 2 points)	Outcome assessment (Max. 1 point)	Adequate follow-up time (Max. 2 points)	Scores and level of evidence
--	------------------------------------	---	--	-----------------------------------	---	------------------------------

**TABLE 4.** SPREADSHEET USED FOR DESCRIBING AND PRESENTING THE RESULTS OF EACH STUDY

Evidence included
Study design
Selected population
Follow-up time
Outcomes considered
Expression of results: percentage, risk, odds, hazard ratio, mean

## RESULTS

### Studies returned (02/2018)

**TABLE 5.** NUMBER OF PAPERS RETURNED FROM THE SEARCH METHODOLOGY USED IN EACH OF THE SCIENTIFIC DATABASES

DATABASE	NUMBER OF PAPERS
Primary	
PubMed-Medline	759
Cochrane	140

### Application of evidence - Recommendation

The recommendations will be elaborated by the authors of the review, with the initial characteristic of synthesis of evidence, is subject to validation by all authors who participated in creating the Guideline.

## REFERENCES

- Paulis G, Brancato T. Inflammatory mechanisms and oxidative stress in Peyronie's disease: therapeutic "rationale" and related emerging treatment strategies. *Inflamm Allergy Drug Targets* 2012;11:48-57.
- Hatzimouratidis K, Eardley I, Giuliano F, Hatzichristou D, Moncada I, Salonia A, et al. EAU guidelines on penile curvature. *Eur Urol*. 2012;62:543-52.
- Nugteren HM, Nijman JM, de Jong IJ, van Driel MF. The association between Peyronie's and Dupuytren's disease. *Int J Impot Res* 2011;23:142-5.
- Tal R, Hall MS, Alex B, Choi J, Mulhall JP. Peyronie's disease in teenagers. *J Sex Med* 2012;9:302-8.
- Kalokairinou K, Konstantinidis C, Domazou M, Kalogeropoulos T, Kosmidis P, Gekas A. US Imaging in Peyronie's Disease. *J Clin Imaging Sci* 2012;2:63.
- Larsen SM, Levine LA. Review of non-surgical treatment options for Peyronie's disease. *Int J Impot Res* 2012;24:1-10.
- Gur S, Limin M, Hellstrom WJ. Current status and new developments in Peyronie's disease: medical, minimally invasive, and surgical treatment options. *Expert Opin Pharmacother* 2011;12:931-44. PMID: 21405946
- LaRochelle JC, Levine LA. A Survey of primary-care physicians and urologists regarding Peyronie's disease. *J Sex Med* 2007;4:1167-73.
- Biagiotti G, Cavallini G. Acetyl-L-carnitine vs. tamoxifen in the oral therapy of Peyronie's disease: a preliminary report. *BJU Int* 2001;88:63-7.
- Teloken C, Rhoden EL, Graziotin TM, Ros CT, Sogari PR, Souto CA. Tamoxifen versus placebo in the treatment of Peyronie's disease. *J Urol* 1999;162:2003-5.
- Park TY, Jeong HG, Park JJ, Chae JY, Kim JW, Oh MM, et al. The efficacy of medical treatment of Peyronie's disease: potassium para-aminobenzoate monotherapy vs. combination therapy with tamoxifen, L-Carnitine, and phosphodiesterase type 5 inhibitor. *World J Mens Health* 2016;34:40-6.
- Weidner W, Hauck EW, Schnitker J; Peyronie's Disease Study Group of Andrological Group of German Urologists. Potassium para-aminobenzoate (POTABA) in the treatment of Peyronie's disease: a prospective, placebo-controlled, randomized study. *Eur Urol* 2005;47:530-5
- Safarinejad MR, Hosseini SY, Kolahi AA. Comparison of vitamin E and propionyl-L-carnitine, separately or in combination, in patients with early chronic Peyronie's disease: a double-blind, placebo-controlled, randomized study. *J Urol* 2007;178:1398-403; discussion 1403. PMID: 17706714.
- Inal T, Tokatli Z, Akand M, Ozdiler E, Yaman O. Effect of intralesional interferon-alpha 2b combined with oral vitamin E for treatment of early stage Peyronie's disease: a randomized and prospective study. *Urology*. 2006;67:1038-42. Epub 2006 Apr 11. PMID: 16581113
- Paulis G, Brancato T, D'Ascenzo R, De Giorgio G, Nupieri P, Orsolini G, et al. Efficacy of vitamin E in the conservative treatment of Peyronie's disease: legend or reality? A controlled study of 70 cases. *Andrology* 2013;1:120-8. PMID: 23258640
- Cakan M, Demirel F, Aldemir M, Altug U. Does smoking change the efficacy of combination therapy with vitamin E and colchicines in patients with early-stage Peyronie's disease? *Arch Androl* 2006;52:21-7. PMID: 16338865
- Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, et al. Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J Med* 2001;29;345:1583-92. PMID: 11757504
- Gelbard M, Goldstein I, Hellstrom WJ, McMahon CG, Smith T, Tursi J, Jones N, et al. Clinical efficacy, safety and tolerability of collagenase clostridium histolyticum for the treatment of peyronie disease in 2 large double-blind, randomized, placebo controlled phase 3 studies. *J Urol* 2013 ;190:199-207. PMID: 23376148
- Lipshultz LI, Goldstein I, Seftel AD, Kaufman GJ, Smith TM, Tursi JP, et al. Clinical efficacy of collagenase Clostridium histolyticum in the treatment of Peyronie's disease by subgroup: results from two large, double-blind,

The available evidence will follow some principles of exposure: it will be by the outcome and will have as components: number of patients, type of comparison, magnitude, and precision (standard deviation and 95% CI).

Its strength will be estimated (Oxford<sup>36</sup>/Grade<sup>40</sup>) as 1b and 1c (grade A) or strong, and as 2a, 2b and 2c (grade B) or moderate weak, or very weak.

### Conflict of interest

There is no conflict of interest related to this review that can be declared by any of the authors.

### Final declaration

The Guidelines Project, an initiative of the Brazilian Medical Association in partnership with the Specialty Societies, aims to reconcile medical information in order to standardize approaches that can aid the physician's reasoning and decision-making process. The information contained in this project must be submitted to the evaluation and criticism of the physician responsible for the conduct to be followed, given the reality and clinical condition of each patient.



- randomized, placebo-controlled, phase III studies. *BJU Int* 2015;116:650-6. PMID: 25711400.
20. Carson CC 3rd, Sadeghi-Nejad H, Tursi JP, Smith TM, Kaufman GJ, Gilbert K, et al. Analysis of the clinical safety of intralesional injection of collagenase Clostridium histolyticum (CCH) for adults with Peyronie's disease (PD). *BJU Int* 2015;116:815-22. PMID: 25818264
  21. Nguyen HMT, Anaissie J, DeLay KJ, Yafi FA, Sikka SC, Hellstrom WJG. Safety and Efficacy of Collagenase Clostridium histolyticum in the Treatment of Acute-Phase Peyronie's Disease. *J Sex Med* 2017;14:1220-1225. PMID: 28874331
  22. Hellstrom WJ, Kendirci M, Matern R, Cockerham Y, Myers L, Sikka SC, et al. Single-blind, multicenter, placebo controlled, parallel study to assess the safety and efficacy of intralesional interferon alpha-2B for minimally invasive treatment for Peyronie's disease. *J Urol* 2006;176:394-8. PMID: 16753449
  23. Kendirci M, Usta MF, Matern RV, Nowfar S, Sikka SC, Hellstrom WJ. The impact of intralesional interferon alpha-2b injection therapy on penile hemodynamics in men with Peyronie's disease. *J Sex Med.* 2005;2:709-15. PMID: 16422829
  24. Trost LW, Ates E, Powers M, Sikka S, Hellstrom WJ. Outcomes of intralesional interferon- $\alpha$ 2B for the treatment of Peyronie disease. *J Urol.* 2013;190:2194-9. PMID: 23688848
  25. Stewart CA, Yafi FA, Knoedler M, Mandava SH, McCaslin IR, Sangkum P, et al. Intralesional Injection of Interferon- $\alpha$ 2b Improves Penile Curvature in Men with Peyronie's Disease Independent of Plaque Location. *J Urol* 2015;194:1704-7. PMID: 26144333
  26. Rehman J, Benet A, Melman A. Use of intralesional verapamil to dissolve Peyronie's disease plaque: a long-term single-blind study. *Urology.* 1998 A;51:620-6. PMID: 9586617
  27. Shirazi M, Haghpanah AR, Badiee M, Afrasiabi MA, Haghpanah S. Effect of intralesional verapamil for treatment of Peyronie's disease: a randomized single-blind, placebo-controlled study. *Int Urol Nephrol* 2009;41:467-71. PMID: 19199072
  28. Levine LA, Goldman KE, Greenfield JM. Experience with intraplaque injection of verapamil for Peyronie's disease. *J Urol.* 2002;168:621-5; discussion 625-6. PMID: 12131321
  29. Favilla V, Russo GI, Zucchi A, Siracusa G, Privitera S, Cimino S, et al. Evaluation of intralesional injection of hyaluronic acid compared with verapamil in Peyronie's disease: preliminary results from a prospective, double-blinded, randomized study. *Andrology* 2017;5:771-775. PMID: 28718527
  30. Twidwell J, Levine L. Topical treatment for acute phase Peyronie's disease utilizing a new gel, H-100: a randomized, prospective, placebo-controlled pilot study. *Int J Impot Res* 2016;28:41-5. PMID: 26700214
  31. Di Stasi SM, Giannantoni A, Stephen RL, Capelli G, Giurioli A, Jannini EA, et al. A prospective, randomized study using transdermal electromotive administration of verapamil and dexamethasone for Peyronie's disease. *J Urol* 2004;171:1605-8. PMID: 15017231
  32. Greenfield JM, Shah SJ, Levine LA. Verapamil versus saline in electromotive drug administration for Peyronie's disease: a double-blind, placebo controlled trial. *J Urol* 2007;177:972-5. PMID: 17296390 (B)
  33. Fojecki GL, Tiessen S, Osther PJ. Extracorporeal shock wave therapy (ESWT) in urology: a systematic review of outcome in Peyronie's disease, erectile dysfunction and chronic pelvic pain. *World J Urol* 2017;35:1-9. PMID: 27108421
  34. Gao L, Qian S, Tang Z, Li J, Yuan J. A meta-analysis of extracorporeal shock wave therapy for Peyronie's disease. *Int J Impot Res* 2016;28:161-6. PMID: 27250868
  35. Furlow WL, Swenson HE Jr, Lee RE. Peyronie's disease: a study of its natural history and treatment with orthovoltage radiotherapy. *J Urol.* 1975;114:69-71. PMID: 1142503
  36. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17:1-12
  37. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B et al. Grading strength of recommendations and quality of evidence in clinical guidelines: report from an american college of chest physicians task force. *Chest* 2006;129(1):174-81. PMID: 16424429
  38. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol* 2009; 62:1013-20. PMID: 19230606 ([http://amstar.ca/Amstar\\_Checklist.php](http://amstar.ca/Amstar_Checklist.php))
  39. Wells G, Shea B, O'Connell D, Robertson J, Peterson J, Welch V, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Disponivel em: [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).
  40. Levels of Evidence and Grades of Recommendations - Oxford Centre for Evidence Based Medicine. Disponivel em <http://www.cebm.net/blog/2009/06/11/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>

