Title
Peyronie's Disease: AUA Guideline

Journal
Investigative Urology, 194(3)

ISSN
0021-0005

Authors
Nehra, Ajay
Alterowitz, Ralph
Culkin, Daniel J
et al.

Publication Date
2015-09-01

DOI
10.1016/j.juro.2015.05.098

Peer reviewed

HHS Public Access

Author manuscript

J Urol. Author manuscript; available in PMC 2016 September 19.

Published in final edited form as:

J Urol. 2015 September ; 194(3): 745–753. doi:10.1016/j.juro.2015.05.098.

Peyronie's Disease: AUA Guideline

Ajay Nehra, **Ralph Alterowitz**, **Daniel J. Culkin**, **Martha M. Faraday**, **Lawrence S. Hakim**, **Joel J. Heidelbaugh**, **Mohit Khera**, **Erin Kirkby**, **Kevin T. McVary**, **Martin M. Miner**, **Christian J. Nelson**, **Hossein Sadeghi-Nejad**, **Allen D. Seftel**, **Alan W. Shindel**, and **Arthur L. Burnett**

American Urological Association Education and Research, Inc., Linthicum, Maryland

Abstract

Purpose—The purpose of this guideline is to provide a clinical framework for the diagnosis and treatment of Peyronie's disease.

DISCLAIMER

This document was written by the Peyronie's Disease Guidelines Panel of the American Urological Association Education and Research, Inc., which was created in 2013. The Practice Guidelines Committee (PGC) of the AUA selected the committee chair. Panel members were selected by the chair. Membership of the committee included representatives of urology, family medicine, clinical psychology, patient advocacy, and other clinicians with specific expertise on this disorder. The mission of the committee was to develop recommendations that are analysis-based or consensus-based, depending on Panel processes and available data, for optimal clinical practices in the diagnosis and treatment of Peyronie's Disease.

Funding of the committee was provided by the AUA. Committee members received no remuneration for their work. Each member of the committee provides an ongoing conflict of interest disclosure to the AUA.

While these guidelines do not necessarily establish the standard of care, AUA seeks to recommend and to encourage compliance by practitioners with current best practices related to the condition being treated. As medical knowledge expands and technology advances, the guidelines will change. Today these evidence-based guidelines statements represent not absolute mandates but provisional proposals for treatment under the specific conditions described in each document. For all these reasons, the guidelines do not pre-empt physician judgment in individual cases.

Treating physicians must take into account variations in resources, and patient tolerances, needs, and preferences. Conformance with any clinical guideline does not guarantee a successful outcome. The guideline text may include information or recommendations about certain drug uses ('off label') that are not approved by the Food and Drug Administration (FDA), or about medications or substances not subject to the FDA approval process. AUA urges strict compliance with all government regulations and protocols for prescription and use of these substances. The physician is encouraged to carefully follow all available prescribing information about indications, contraindications, precautions and warnings. These guidelines and best practice statements are not intended to provide legal advice about use and misuse of these substances.

Although guidelines are intended to encourage best practices and potentially encompass available technologies with sufficient data as of close of the literature review, they are necessarily time-limited. Guidelines cannot include evaluation of all data on emerging technologies or management, including those that are FDA-approved, which may immediately come to represent accepted clinical practices.

For this reason, the AUA does not regard technologies or management which are too new to be addressed by this guideline as necessarily experimental or investigational.

CONFLICT OF INTEREST DISCLOSURES

All panel members completed COI disclosures. Relationships that have expired (more than one year old) since the panel's initial meeting, are listed. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received. **Consultant/Advisor: Ralph Alterowitz, MEA**, The Center for Intimacy After Cancer Therapy Inc. (U); **Mohit Khera, MD**, Coloplast (C); American Medical Systems (C); Endo Pharmaceuticals (C); **Kevin T. McVary, MD**, Watson Pharmaceuticals (C), Lilly/ICOS (C), **Health Publishing: Arthur L. Burnett II, MD**, Urology Times Editorial Council (C); VIVUS (C); **Alan W. Shindel, M.D.**, Endotext.com (C), International Society for Sexual Medicine (C) **Leadership Position: Ralph Alterowitz, MEA**, The Center for Intimacy After Cancer Therapy Inc. (U); **Alan W. Shindel, M.D.**, Sexual Medicine Society of North America (C) **Meeting Participant or Lecturer: Ralph Alterowitz, MEA**, The Center for Intimacy After Cancer Therapy Inc. (U); **Kevin T. McVary, MD**, Watson Pharmaceuticals (C), Lilly/ICOS (C), **Lawrence S. Hakim, MD**, ENDO Urology (C), Slate/ Auxilium (C) **Scientific Study or Trial: Arthur L. Burnett II, MD**, Acorda Therapeutics (C); Endo Pharmaceuticals (C); Pfizer (C); Auxilium Inc. (C); American Medical Systems (C); Coloplast (C); Astellas (C); Reflexonic LLC (C); VIVUS (C); **Kevin T. McVary, MD**, Astellas (C), Lilly/ICOS (C), NxThera (U), American Medical Systems (C), Sophris (C); **Hossein Sadeghi-Nejad, MD**, Endo Pharmaceuticals/Auxilium (C) **Other: Kevin T. McVary, MD**, Lilly/ICOS, Principal Investigator (C), NIDDK, Principal Investigator (C), **Christian J. Nelson, PhD**, American Medical Systems (U).

Materials and Methods—A systematic review of the literature using the PubMed®, EMBASE® and Cochrane databases (search dates 1/1/1965 to 1/26/15) was conducted to identify peer-reviewed publications relevant to the diagnosis and treatment of PD. The review yielded an evidence base of 303 articles after application of inclusion/exclusion criteria.

Results—The systematic review was used to create guideline statements regarding treatment of PD. When sufficient evidence existed, the body of evidence for a particular treatment was assigned a strength rating of A (high quality evidence; high certainty), B (moderate quality evidence; moderate certainty), or C (low quality evidence; low certainty). Evidence-based statements of Strong, Moderate, or Conditional Recommendation were developed based on benefits and risks/burdens to patients. Additional consensus statements related to the diagnosis of PD are provided as Clinical Principles and Expert Opinions due to insufficient published evidence.

Conclusions—There is a continually expanding literature on PD; the Panel notes that this document constitutes a clinical strategy and is not intended to be interpreted rigidly. The most effective approach for a particular patient is best determined by the individual clinician and patient in the context of that patient's history, values, and goals for treatment. As the science relevant to PD evolves and improves, the strategies presented here will be amended to remain consistent with the highest standards of clinical care.

Keywords

penis; fibrosis; penile induration

BACKGROUND

Definition

The Panel defines Peyronie's disease as an acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, deformity, erectile dysfunction, and/or distress.

Epidemiology

Findings regarding prevalence rates range from 0.5 to 20.3% within specific populations and depend on the methodology employed, the sample under study, how PD is defined, and how men are queried. Rates may be higher among men who present with comorbidities. More recent studies suggest that prevalence rates have been historically under-estimated, suggesting a greater awareness of the disease and its symptoms currently.

Pathophysiology

Microvascular trauma to the penile shaft associated with penile buckling in the erect or semi-erect state secondary to sexual activity is thought to be the most common inciting event; however, many patients do not recall an incident that preceded symptom onset. It is hypothesized, however, that repetitive minor trauma to the penis initiates a cascade involving significant extravascular protein deposition, fibrin trapping, macrophage recruitment, cytokine overexpression, and release of elastase, leading to changes in the tunical collagen from type 1 to a predominant type 3.[1–4]

Natural History

PD is characterized by symptoms with a variable course, some of which may improve or resolve without treatment in some patients. Data suggest that for many or most patients, pain will resolve over time without intervention. Curvature and other types of deformity are less likely to resolve, although younger men and those with symptoms present for less than six months may experience some improvement. Treatment of persistent deformity may be required if it compromises sexual function and/or causes distress for the patient and/or his partner.

Impact on Psychosocial Functioning and Quality of Life

Many men with PD experience emotional distress, depressive symptoms, and relationship difficulties.[5] These depressive symptoms remain consistently high over time, suggesting PD has a lasting psychological impact.[6] The stress of PD often extends to men's relationships, with 54% of men reporting relationship difficulties as a result of PD.[7] Men express concerns about the physical appearance of their penis and report PD negatively impacts their masculine self-image and sexual satisfaction.[8] They report increased anxiety in sexual situations, decreased sexual confidence, and a concern that they are not satisfying their partners.[8] Additionally, men with PD report a sense of isolation as they find it difficult to communicate with their healthcare professionals or partners about PD.[8]

Literature Limitations

The changing nature of PD symptoms and the possibility that improvement in some patients may occur with the passage of time makes the study of treatment effects challenging. Some symptoms, such as pain, are highly susceptible to placebo effects. Observational studies cannot control for either of these issues. In addition, many studies rely on patient perceptions of changes in deformity and penile dimensions as primary outcomes. The correlation between subjective and objective measures of deformity and penile dimensions, however, is limited.

PATIENT PRESENTATION

Symptoms

The most common presentation is the male in his mid-50s who presents with recent onset of penile curvature accompanied by mild to moderate penile pain. The patient usually doesn't recall a specific sexual or non-sexual event that preceded symptom onset. Generally his erection is still firm enough for intercourse. The penile curvature, however, may either preclude intercourse or make intercourse difficult for the patient and/or his partner. The patient and clinician usually cannot palpate any abnormalities on the penile shaft in the non-erect state. Penile curvature and varying degrees of penile pain may be considered diagnostic, although rare pathologies (e.g., penile tumors) must be excluded.

Active vs. Stable Disease

It is useful clinically to distinguish between active and stable disease because treatment options differ.

Active disease—Active disease is characterized by dynamic and changing symptoms. Penile and/or glanular pain or discomfort with or without erection is the defining symptom of the active stage. Symptom onset may be associated with a history of penile injury during intercourse. The patient may or may not manifest the presence of penile induration. Plaque(s) and penile deformities may not be fully developed at this stage. Distress may be present in response to pain and to progressive deformity. Erectile function may be intact or may be compromised by pain and/or developing deformity.

Stable disease—In the patient with stable disease, symptoms have been clinically unchanged for at least three months based on either patient report or clinician documentation. Pain with or without erection may rarely be present but is typically mild. Curvature may be uniplanar or biplanar and may not be dependent on the size and magnitude of the plaque. Plaque(s) may be palpable or apparent on ultrasound. The typical patient presents with a dorsal, dorso-lateral, or ventral penile deformity.

Please refer to the figure for the diagnosis and treatment algorithm.

GUIDELINE STATEMENTS

Insufficient literature was identified to constitute an evidence base for diagnosis of PD in clinical practice. This section provides a framework for determining whether a diagnosis of PD is appropriate.

Diagnosis

1 Clinicians should engage in a diagnostic process to document the signs and symptoms that characterize Peyronie's disease. The minimum requirements for this examination are a careful history (to assess penile deformity, interference with intercourse, penile pain, and/or distress) and a physical exam of the genitalia (to assess for palpable abnormalities of the penis). *(Clinical Principle)*

The clinician should meticulously elicit the patient's history of penile symptoms, including onset, precipitating factors, duration, changes over time, prior treatments used, and other conditions (e.g., ED) that may affect treatment options. A careful examination of the genitalia should be performed that includes stretching and palpation of the flaccid penis and documentation of circumcision status and any anomalies (e.g., hypospadias).

2 Clinicians should perform an in-office intracavernosal injection (ICI) test with or without duplex Doppler ultrasound prior to invasive intervention. *(Expert Opinion)*

The ICI test enables assessment of penile deformity, plaque(s), and pain in the erect state. When the ICI test is combined with duplex ultrasound, additional measurements of plaque size and/or density can be made, calcified and non-calcified plaques can be differentiated, and information on the vascular integrity of the penis can be obtained.

3 Clinicians should evaluate and treat a man with Peyronie's disease only when they have the experience and diagnostic tools to appropriately evaluate, counsel, and treat the condition. *(Expert Opinion)*

Treatment

PD is a symptom complex that may compromise sexual function and QoL but does not appear to affect survival. For some patients, thoughtful counseling regarding the nature of PD and the typical disease course may be sufficient to alleviate concerns, and a patient may choose not to pursue further treatment.

4 Clinicians should discuss with patients the available treatment options and the known benefits and risks/burdens associated with each treatment. *(Clinical Principle)*

To optimize effectiveness of and patient satisfaction with any treatment for PD, it is critical for patients to have realistic expectations regarding the likely magnitude of treatment effects and the probability and type of adverse events. With this context in mind, clinicians should carefully review the potential benefits and risks/burdens of each treatment option.

5 Clinicians may offer oral non-steroidal anti-inflammatory medications to the patient suffering from active Peyronie's disease who is in need of pain management. *(Expert Opinion)*

Patient pain level can be assessed using a visual analog scale and managed with oral non-steroidal anti-inflammatory agents. Pain level should be periodically reassessed to measure treatment efficacy.

6 Clinicians should not offer oral therapy with vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or a combination of vitamin E with L-carnitine. [*Moderate Recommendation; Evidence Strength Grade B (vitamin E)/B (omega-3 fatty acids)/B (Vitamin E + propionyl-L-carnitine)/ C(tamoxifen)/C(procarbazine)*]

There is no convincing evidence for the efficacy of any of the listed therapies. In the Panel's judgment, the use of therapies without proven efficacy, even in the absence of significant adverse events, constitutes a moderate risk/burden in terms of postponing or pre-empting the use of other efficacious treatments, the inability to alleviate patient distress, the time expended on treatments that do not work, and the costs associated with these medications or substances. Further, the Panel notes that oral therapies are not appropriate for patients with stable disease.

7 Clinicians should not offer electromotive therapy with verapamil. *(Moderate Recommendation; Evidence Strength Grade C)*

One randomized-controlled trial[9] and one observational study[10] evaluated verapamil delivered via electromotive drug administration. In the RCT, electromotive verapamil (delivered at home) provided minimal benefit compared to placebo with the two groups statistically indistinguishable with regard to curvature decreases and the percent of patients who improved.

8 Clinicians may administer intralesional collagenase clostridium histolyticum in combination with modeling by the clinician and by the patient for the reduction of penile curvature in patients with stable Peyronie's disease, penile curvature

>30° and <90°, and intact erectile function (with or without the use of medications). *(Moderate Recommendation; Evidence Strength Grade B)*

Intralesional collagenase is a therapy for curvature; it does not treat pain or ED. IMPRESS I and II are the definitive trials that established the current FDA-approved intralesional collagenase plus modeling protocol.[11] The trials focused on up to eight injections of 10,000 U over 24 weeks, and followed patients for an additional 7.5 months after treatment for a total follow up duration of one year. All patients experienced modeling, which was performed by the clinician after each treatment cycle. Patients were instructed to perform modeling at home three times/day between treatment cycles and to attempt to straighten the penis without pain during spontaneous erections once daily.

Patients had average PD symptom durations of 57.6 and 40.8 months in the placebo groups and of 46.8 and 50.4 months in the collagenase groups. Average baseline curvature was 49.0° and 49.6° in the placebo groups and 48.8° and 51.3° in the collagenase groups. At one year of follow-up, curvature was reduced by mean 17° in the collagenase groups; curvature was reduced by mean 9.3° in the placebo groups. Note this is a modest difference of 7.7°.

9 Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional collagenase regarding potential occurrence of adverse events, including penile ecchymosis, swelling, pain, and corporal rupture. *(Clinical Principle)*

In the IMPRESS trials, 84.2% of patients in the collagenase groups and 36.3% of patients in the placebo groups experienced at least one adverse event after up to four treatment cycles. The most common adverse events were penile ecchymosis, penile swelling, and penile pain. Most adverse events were considered mild or moderate by the investigators and resolved without intervention.

10 Clinicians may administer intralesional interferon α-2b in patients with Peyronie's disease. *(Moderate Recommendation; Evidence Strength Grade C)*

One multicenter RCT (reported on by Hellstrom et al.[12] and Kendirci et al.[13]) evaluating intralesional interferon α-2b required that patients had PD symptoms for >12 months with curvature of at least 30°. Patients were administered 5 MU interferon α-2b every 2 weeks for 12 weeks compared to placebo. Curvature, plaque size, penile pain, erectile function (with the International Index of Erectile Function), and penile hemodynamics were measured at baseline and at study completion. Statistically significant improvements were documented, including curvature reduction (interferon 13.5°, placebo=4.5°); plaque size reduction (interferon=2.6 cm^2, placebo=0.9 cm^2); penile pain resolution (interferon=67.7%, placebo=28.1%). Additionally, penile duplex Doppler ultrasound revealed significant improvements in peak systolic velocity and mean resistive index in the interferon group but not in the placebo group.

An additional randomized design by Inal et al. compared vitamin E 400 IU twice daily for 24 weeks, interferon 5 MU weekly for 12 weeks, and interferon 5 MU weekly (for 12 weeks) + vitamin E 400 IU twice daily (for 24 weeks).[14] In contrast to the placebo-controlled RCT, this study did not document statistically significant improvement in any

measured parameter, including curvature, plaque size or pain. However, there are important differences in the patient population evaluated. In this study, patients had early stage PD of <6 months duration in contrast to the RCT patients who had average symptom duration of 20 months and are hence likely to have had stable disease. The Panel interpreted these findings to indicate that intralesional interferon is most appropriate for the patient with stable disease.

11 Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional interferon α-2b about potential adverse events, including sinusitis, flu-like symptoms, and minor penile swelling. *(Clinical Principle)*

Such symptoms can be effectively treated with over-the-counter nonsteroidal anti-inflammatory medications and typically last <48 hours. Oral hydration is helpful to mitigate these transient symptoms.

12 Clinicians may offer intralesional verapamil for the treatment of patients with Peyronie's disease. *(Conditional Recommendation; Evidence Strength Grade C)*

The evidence for the use of intralesional verapamil is weak; clinicians should carefully consider whether use of this treatment is appropriate given the substantial uncertainty regarding its efficacy and the availability of other treatments that are clearly more effective. The literature is challenging to interpret given the varied patient inclusion criteria, including the focus on patients in the active disease stage with dynamic and evolving symptoms; varied treatment protocols; and the conflicting findings reported.

13 Clinicians should counsel patients with Peyronie's disease prior to beginning treatment with intralesional verapamil about potential adverse events, including penile bruising, dizziness, nausea, and pain at the injection site. *(Clinical Principle)*

14 Clinicians should not use extracorporeal shock wave therapy (ESWT) for the reduction of penile curvature or plaque size. *(Moderate Recommendation; Evidence Strength Grade B)*

In randomized trials, patient inclusion criteria varied considerably with treatment durations ranging from four to six weeks with typically one session per week. The number of shock waves ranged from 2,000 to 3,000, and the mJ per mm^2 ranged from 0.25 to 0.29.

Chitale et al.[15] reported no effects of ESWT to improve curvature and/or plaque size. Hatzichristodoulou et al.[16] reported that curvature was reduced similarly in the active and sham treatment groups, with statistically similar percentages of patients experiencing improvement and worsening of curvature and plaque. Palmieri et al. (2009)[17] reported small non-significant decreases in curvature and plaque for the ESWT group and small increases in curvature and plaque for the placebo/sham group. Palmieri et al. (2012),[18] which compared ESWT to ESWT + tadalafil, reported similar small curvature and plaque decreases for both groups.

15 Clinicians may offer extracorporeal shock wave therapy (ESWT) to improve penile pain. *(Conditional Recommendation; Evidence Strength Grade B)*

Hatzichristodoulou et al. and Palmieri et al. (2009) similarly reported that mean pain scores on a visual analog scale decreased more among ESWT patients than among placebo/sham patients. Palmieri et al. (2012), which compared ESWT to ESWT + tadalafil, reported similar large pain level decreases in both groups.

The Panel notes that penile pain commonly resolves over time, and ESWT may pose a substantial patient burden. As such, it is the opinion of the Panel that the overall utility of ESWT in the management of PD is low.

16 Clinicians should not use radiotherapy (RT) to treat Peyronie's disease. *(Moderate Recommendation; Evidence Strength Grade C)*

A wide range of RT doses was used in the observational studies reviewed, ranging from 2.2 Gy to 45 Gy, generally administered in 1.5 to 2.0 Gy fractions. Furlow et al.[19] provided data on 2 RT doses (1 treatment of 2.2 to 5.5 Gy vs. 2 treatments with total 4.4 to 10.4 Gy) and a no-treatment comparison group.

With regard to effects on curvature, Furlow et al. noted that rates of curvature improvement were similar across the two RT groups (50% and 39%) and the no treatment control group (52%). In terms of plaque improvement, improvement rates for the RT groups (55% and 44%) were essentially the same as for the no treatment control group (58%). Furlow et al. further reported that pain improvement rates were indistinguishable across the two RT groups (100% and 92.3%) and the no treatment control group (100%).

Given the potential risks of exposing patients to RT in the context of unproven benefits, the Panel interpreted these data to mean that RT should not be offered to patients with PD. Further, the information provided by Furlow et al. suggests that any changes in symptoms may be readily attributable to the passage of time.

17 Clinicians should assess patients as candidates for surgical reconstruction based on the presence of stable disease. *(Clinical Principle)*

Typically, PD lesions become stable at 12 to 18 months after symptom onset. The most common inclusion criteria for surgical studies are the presence of PD symptoms for at least 12 months and stable curvature for 3 to 6 months. This literature focuses almost entirely on patients with stable disease; surgical outcomes for patients with active disease are not known.

18 Clinicians may offer tunical plication surgery to patients whose rigidity is adequate for coitus (with or without pharmacotherapy and/or vacuum device therapy) to improve penile curvature. *(Moderate Recommendation; Evidence Strength Grade C)*

Tunical plication is the most common surgical strategy used to treat PD patients, representing approximately half of all surgeries conducted on PD patients who undergo reconstruction. The most commonly-reported outcome was curvature improvement post-surgery, which occurred in a majority of studies at a rate of 90% or higher.

Because plication surgery is not a treatment for ED and because the consequences of plication surgery with regard to erectile function remain unclear, the most appropriate candidates for plication surgery are patients with intact erectile function or with ED responsive to oral medications or vacuum pump therapy or ICI therapy.

19 Clinicians may offer plaque incision or excision and/or grafting to patients with deformities whose rigidity is adequate for coitus (with or without pharmacotherapy and/or vacuum device therapy) to improve penile curvature. *(Moderate Recommendation; Evidence Strength Grade C)*

Similar to other surgical procedures, the most commonly-reported outcome following plaque incision and/or excision with grafting was curvature improvement, which generally ranged from 25% to 100% with a majority of study arms reporting rates >80%.

The Panel notes that, for most patients, plaque incision and/or excision with grafting results in curvature correction in the setting of a relatively low risk of serious adverse events. As with plication, the most appropriate candidates for this procedure are patients with intact erectile function or ED responsive to oral medications or vacuum pump therapy.

20 Clinicians may offer penile prosthesis surgery to patients with Peyronie's disease with erectile dysfunction (ED) and/or penile deformity sufficient to prevent coitus despite pharmacotherapy and/or vacuum device therapy. *(Moderate Recommendation; Evidence Strength Grade C)*

The literature in this area is challenging to interpret given the small sample sizes and diversity of surgical techniques and prostheses employed. In addition to prosthesis implantation, most studies used other surgical procedures, including modeling, plication, plaque incision or excision, tunica albuginea incision, and/or grafts of various materials. Curvature improvement post-surgery was reported at >80% in all studies reviewed.

21 Clinicians may perform adjunctive intraoperative procedures, such as modeling, plication or incision/grafting, when significant penile deformity persists after insertion of the penile prosthesis. *(Moderate Recommendation; Evidence Strength Grade C)*

A majority of prosthetic surgery studies reviewed utilized intraoperative procedures, such as modeling, plication, plaque incision or excision, TA incision, and/or grafting as adjunctive techniques to prosthesis insertion to achieve optimal curvature correction and penile dimensions. Adjunctive procedures are frequently necessary to achieve patient and clinician goals for prosthesis surgery; the available adverse event evidence suggests no correlation between surgical complexity and infection or revision rates or patient satisfaction.

22 Clinicians should use inflatable penile prosthesis for patients undergoing penile prosthetic surgery for the treatment of Peyronie's disease. *(Expert Opinion)*

The Panel notes that modeling to maximize curvature correction is difficult to accomplish with semi-rigid devices. Given that it is not possible to know whether modeling is needed until the operation begins, the choice of a prosthesis that allows modeling is optimal.

OTHER TREATMENTS

The Panel identified the treatments listed in the table as having insufficient evidence to support even a Conditional Recommendation. In the Panel's view, the treatments in this category are unproven until a larger and/or more rigorous evidence base is available.

RESEARCH NEEDS AND FUTURE DIRECTIONS

Given its prevalence and significant psychosocial impact, better understanding of the pathophysiology of PD is greatly needed and is critical for development of clinical therapies that are effective and safe. The absence of knowledge regarding what causes PD has two major consequences: it is not possible to advise men regarding risk factors and how the disease may be prevented, and treatments remain focused on the alleviation of symptoms rather than on causal mechanisms. Ideally, future treatments will be developed with full understanding of the scientific basis of the disease and that demonstrate consistent clinical effectiveness for most or all patients. Research endeavors in this field should continue to address multiple disciplinary areas including epidemiology, risk associations, pathophysiology, psychosocial assessment, diagnostics, clinical pharmacology and therapeutics, and health-related outcomes. Clinical studies should be designed to control for PD natural history, account for placebo effects, and employ valid measures of relevant outcomes.

Abbreviations and Acronyms

ED	erectile dysfunction
EMDA	electromotive drug administration
ESWT	extracorporeal shock wave therapy
ICI	intracavernosal injection
IIEF	International Index of Erectile Function
PD	Peyronie's disease
QoL	quality of life
RCT	randomized-controlled trial
RT	radiotherapy
VAS	visual analog scale

References

1. Haag SM, Hauck EW, Eickelberg O, et al. Investigation of the antifibrotic effect of IFN-gamma on fibroblasts in a cell culture model of Peyronie's disease. Eur Urol. 2008; 53:425. [PubMed: 17630104]
2. Mulhall JP. Expanding the paradigm for plaque development in Peyronie's disease. Int J Impotence Res. 2003; 15:S93.

3. Somers KD, Sismour EN, Wright GL Jr, et al. Isolation and characterization of collagen in Peyronie's disease. J Urol. 1989; 141:629. [PubMed: 2918606]
4. Somers KD, Dawson DM. Fibrin deposition in Peyronie's disease plaque. J Urol. 1997; 157:311. [PubMed: 8976287]
5. Nelson CJ, Mulhall JP. Psychological impact of Peyronie's disease: a Review. J Sex Med. 2013; 10:653. [PubMed: 23153101]
6. Nelson CJ, Diblasio C, Kendirci M, et al. The chronology of depression and distress in men with Peyronie's disease. J Sex Med. 2008; 5:1985. [PubMed: 18554257]
7. Smith JF, Walsh TJ, Conti SL, et al. Risk factors for emotional and relationship problems in Peyronie's disease. J Sex Med. 2008; 5:2179. [PubMed: 18638001]
8. Rosen R, Catania J, Lue T, et al. Impact of Peyronie's disease on sexual and psychosocial functioning: qualitative findings in patients and controls. J Sex Med. 2008; 5:1977. [PubMed: 18564146]
9. 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; 177:3972.
10. Pirozzi-Farina F, Curreli A, Deriu M, et al. Ultrasonographic findings in the medical treatment of I.P.P.: our indications. Acta Urologica Italica. 1997; 11:6459.
11. Gelbard M, Goldstein I, Hellstrom WJ, 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; 190:1199.
12. Hellstrom WJ, Kendirci M, Matern R, 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; 176:1394.
13. Kendirci M, Usta MF, Matern RV, et al. The impact of intralesional interferon alpha-2b injection therapy on penile hemodynamics in men with Peyronie's disease. J Sex Med. 2005; 2:709. [PubMed: 16422829]
14. Inal T, Tokatli Z, Akand M, et al. 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; 67:51038.
15. Chitale S, Morsey M, Swift L, et al. Limited shock wave therapy vs sham treatment in men with Peyronie's disease: results of a prospective randomized controlled double-blind trial. BJU Int. 2010; 106:1352. [PubMed: 20438568]
16. Hatzichristodoulou G, Meisner C, Gschwend JE, et al. Extracorporeal shock wave therapy in Peyronie's disease: results of a placebo-controlled, prospective, randomized, single-blind study. J Sex Med. 2013; 10:2815. [PubMed: 23898925]
17. Palmieri A, Imbimbo C, Longo N, et al. A first prospective, randomized, double-blind, placebo-controlled clinical trial evaluating extracorporeal shock wave therapy for the treatment of Peyronie's disease. Eur Urol. 2009; 56:2363.
18. Palmieri A, Imbimbo C, Creta M, et al. Tadalafil once daily and extracorporeal shock wave therapy in the management of patients with Peyronie's disease and erectile dysfunction: results from a prospective randomized trial. Int J Androl. 2012; 35:2190.
19. Furlow WL, Swenson HE Jr, Lee RE. Peyronie's disease: a study of its natural history and treatment with orthovoltage radiotherapy. J Urol. 1975; 114:169.

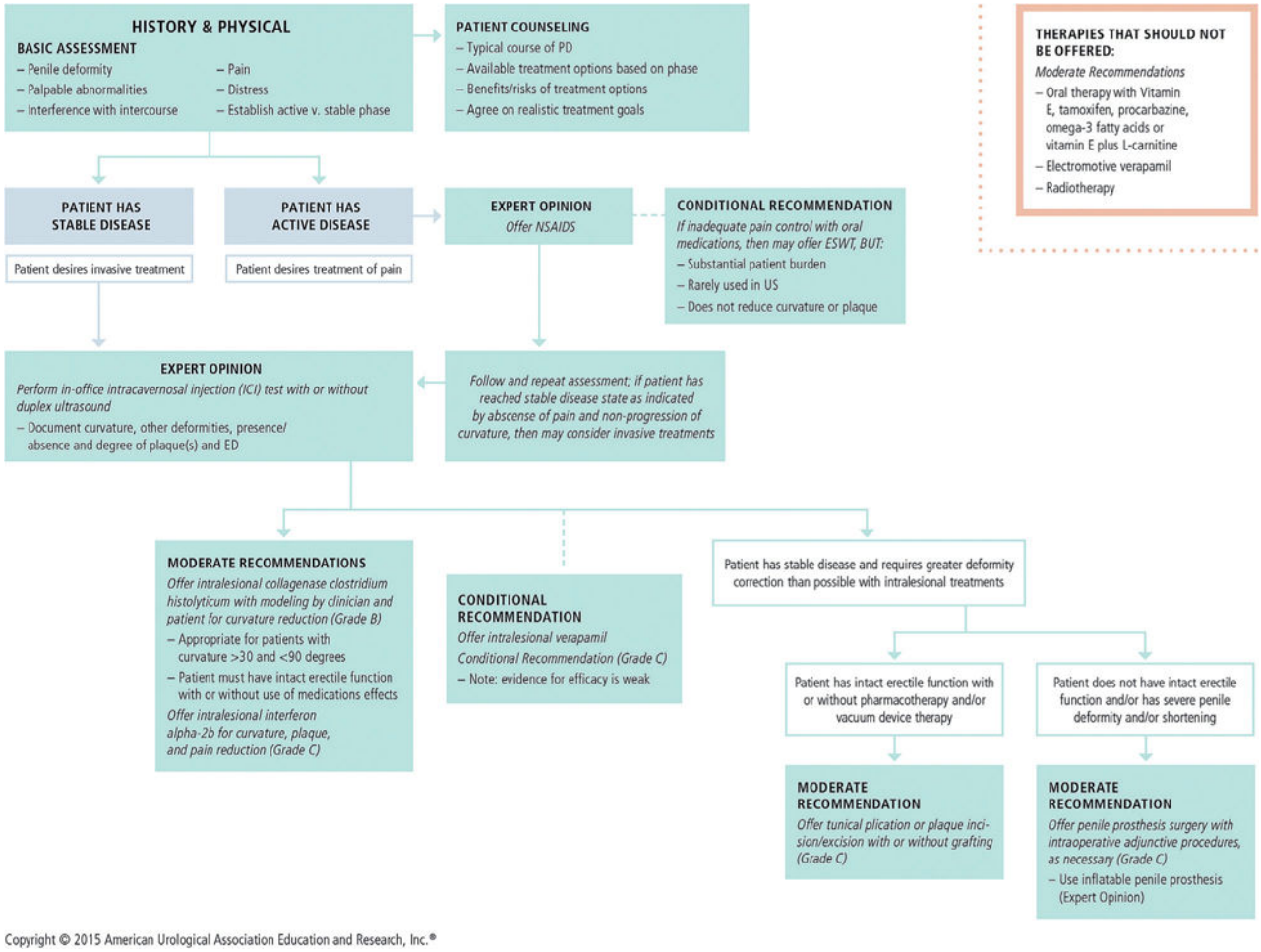

Figure.
Peyronie's disease diagnosis and treatment algorithm

Table

Other Treatments

Oral Therapies
Colchicine
Pentoxifylline
Potassium aminobenzoate
Co-enzyme Q10
Topical Therapies
Magnesium or verapamil
Liposomal recombinant human superoxide dismutase (LrhSOD)
Intralesional Therapies
Intralesional LrhSOD
Nicardipine
Parathyroid hormone
Dexamethasone
Betamethasone + hyaluronidase + lidocaine
Iloprost
Verapamil with or without intralesional dexamethasone and with or without lidocaine electromotive
Electromotive Therapies
Electromotive verapamil + dexamethasone
Combination Therapies
Verapamil intralesional + oral L-carnitine
Verapamil intralesional + oral tamoxifen
Interferon intralesional + oral vitamin E
Verapamil intralesional + oral l-arginine + oral pentoxifylline
Verapamil intralesional + oral l-arginine + oral pentoxifylline + penile traction
Oral vitamin E with or without ICI treatments (papaverine, phentolamine, PGE1) and with or without oral colchicine
Ultrasound + hydrocortisone
Mechanical Therapies
Penile traction
Vacuum pump without the constriction ring
Hyperthermia