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Comparing and Contrasting Peyronie's Disease Guidelines: Points of Consensus and Deviation

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Introduction:

Peyronie's disease (PD) is a wound-healing disorder of the penis resulting in variable symptoms such as penile pain, deformity, and sexual dysfunction.[1] The true prevalence remains somewhat elusive due to differences in defining the condition, discordance in patient symptom severity and physician perception, and even historical underreporting. Estimates range from 0.4–9% in the general male population, and the prevalence may be as high as 15–20% within certain populations such as those with prostate cancer or diabetes.[2–6] The minority of patients with PD actually seek consultation with a specialist, likely due to symptom heterogeneity, a sense of embarrassment, and lack of awareness by primary care providers and other referring clinicians.[7] However, public awareness seems to be increasing due to greater population health literacy.[8, 9]

PD has a profound impact from both functional (i.e. physical challenges with sexual activity) and emotional standpoints extending to psychological well-being and quality of life.[1, 10, 11] The sense of shame and lack of self-confidence often leads to relationship challenges. [11–15] Intimate partners of men with PD suffer from sexual dysfunction as well. Fortunately both the physical and psychological ramifications may improve with appropriate diagnosis and

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treatment, supporting that clinicians have the potential to greatly improve the quality of life for our patients with PD.[16–19]

A multitude of more and less invasive treatments have been studied with differing levels of evidence. [120] Our ability to rapidly improve upon the treatment armamentarium is limited by inherent challenges with PD research. The published literature is hampered by significant shortcomings in study methodology.[21, 22] Therapeutic goals vary by patient preference and study design, but may include pain control, penile lengthening, curvature or indentation improvement, plaque size reduction, psychological enhancement, and functional improvements such as the ability to engage in more satisfactory sexual intercourse. The challenges are further amplified by our limited understanding of the pathophysiology underlying PD and other fibrotic conditions.[23]

Clinician training, familiarity with treatment options, and practice patterns vary widely.[24, 25] Many clinicians offer therapies with minimal proven efficacy. This may delay or even prevent definitive treatment for our patients who become frustrated or disheartened with the lack of results. To address the known short-comings and enhance patient care, several medical societies have created clinical documents to guide PD diagnosis and treatment.

Within the last five years clinical guidelines were published by the American Urological Association (AUA), International Society for Sexual Medicine (ISSM), Canadian Urological Association (CUA), and the European Association of Urology (EAU).[26–29] Clinical guidelines are important because they provide an evidence-based approach to medical practice. Limitations with the PD literature preclude definitive evidence-based recommendations in many instances, and the panels often rely on expert opinion to supplement their guideline statements. This creates the opportunity for heterogeneity amongst the various guideline recommendations, and lends to ongoing uncertainty for many clinicians who encounter PD in clinical practice. Here, we aim to provide clinicians who may encounter PD in their clinical practice with a comprehensive review and comparison of the published PD clinical guidelines with the specific goals to 1) highlight points of clear consensus, 2) explore areas of controversy, and 3) emphasize future research needs.

Material and Methods:

A search was performed to identify peer-reviewed, evidence-based guidelines for PD diagnosis and treatment. Four clinical practice guidelines were identified and selected for review from the following societies: American Urological Association (AUA), Canadian Urological Association (CUA), European Association of Urology (EAU), and the International Society of Sexual Medicine (ISSM).[Figure 1] All guideline panels performed systematic literature reviews, assigned graded recommendations based on level of evidence when possible, and presented consensus statements where evidence is lacking. All guidelines provide a review of PD epidemiology, pathophysiology, and associated risk factors in addition to recommendations regarding evaluation and management options.

The AUA Peyronie’s Disease Guideline was published in 2015 with the stated aim to “provide direction to clinicians and patients regarding how to recognize Peyronie’s

Disease (PD), conduct a valid diagnostic process, and approach treatment with the goals of maximizing symptom control, sexual function, and patient and partner quality of life while minimizing adverse events and patient and partner burden."[1] The panel consisted of 14 members with expertise in sexual medicine and study methodology. They performed a systematic literature review of the Pubmed, Embase, and Cochrane databases from 1965 to 2015. This yielded 281 articles meeting inclusion criteria that were included in the analysis. Graded recommendations (grades A through C) were assigned based on the level of evidence, and this was supplemented by consensus statements where evidence was lacking. A total of 22 guideline statements were developed encompassing diagnosis (three statements) and treatment (nineteen statements).

In 2015 the ISSM convened the Fourth International Consultation on Sexual Medicine (ICSM) in Madrid, Spain.[28] A panel of ten experts reviewed the published literature through 2015 along with previously published guidelines from the AUA and EAU. The pertinent articles were reviewed during the consultation meeting, and selected articles were used to modify previously agreed upon guideline statements from the third ICSM, which was held in 2009. Levels of evidence were assigned to guideline statements and consensus statements were used to supplement these recommendations where the literature was lacking. Seven guideline summary statements were developed and specific diagnostic and treatment-related recommendations were expanded upon within the published guideline document itself.

The CUA guideline for Peyronie's Disease and congenital penile curvature was published in 2018. The panel, which consisted of six sexual medicine experts, "sought to provide actionable recommendations to guide PD care in the Canadian health system." [26] A systematic literature review was carried out inclusive of articles published through 2017, and the panel excluded pre-clinical studies. Evidence quality was graded based on the International Consultation for Urologic Disease (ICUD)/World Health Organization (WHO) modified Oxford Centre for Evidence-Based Medicine grading system (levels 1–4) and ultimately given a consensus grade of A through D (D=consensus statement or no recommendation possible) in a manner similar to the AUA PD guideline.[1, 26] The panel made note that grade A and B recommendations were rare due to the low evidence quality.[26] Specific guideline recommendations are stated and expanded upon within the document discussion itself, and a treatment algorithm is also included.

Finally, in March 2020 the EAU published guidelines on sexual and reproductive health including a section specific to penile curvature and Peyronie's Disease.[29] This was an update to the previously published EAU guidelines from 2012 and 2017. Twenty experts were included in the guideline panel. They carried out a comprehensive search to expand the literature base including pertinent studies up through 2018. Recommendations were graded based on several criteria including evidence quality, magnitude of effect, result certainty, and patient-specific values. Levels of evidence were determined based on panel consensus and summarized on a scale from 1 to 5. Specific guideline recommendations were characterized as "strong" or "weak" based on expert-opinion, and each statement was expanded upon within the guideline itself.

Guideline Review and Summary

Each of the four guidelines were independently reviewed by three authors (MGM, LAW, MJZ) and pertinent data abstracted for comparison between guidelines. The specific areas of interest (i.e. information obtained in Tables 1–3) were determined a priori. Guideline statements and accompanying discussions within each document were carefully reviewed. In some instances, a clear guideline statement was not specified, but panel recommendations could be ascertained within the text of the guideline discussion. Recommendations pertaining to diagnosis/evaluation, non-surgical treatments, and surgical treatments within each guideline are summarized in Tables 1, 2,and 3, respectively. Panel recommendations were assigned one of four values: (i) “recommended”, (ii) ”may consider”, (iii) “unclear benefits”, or (iv) “recommended against” based on consensus from the manuscript authors. “Not addressed” was included in the pertinent table column if a topic was not discussed or there was no clear recommendation based on careful review of the guideline document.

Of note, statements specifically pertaining to congenital penile curvature were present in the EAU and CUA guideline. [26, 29] This was considered outside the scope of the current review and is not addressed herein.

Results

Definition

PD is similarly described across all guidelines as an acquired penile abnormality associated with pain, deformity, erectile dysfunction (ED), and distress. There is agreement amongst the guideline panels in characterizing the underlying pathophysiology as fibrosis of the tunica albuginea likely caused from aberrant healing incited by repetitive minor trauma. All guideline documents also highlight the potential genetic predisposition with PD, and the newest EAU guidelines from 2020 describe the various genes that have been implicated in PD pathophysiology.[29] EAU and ISSM guidelines describe specific medical comorbidities that have been associated with PD such as Dupuytren’s contracture, diabetes, hypertension, lipid disease, ischemic cardiomyopathy, ED, low testosterone, pelvic surgery, as well as tobacco and alcohol use.[28, 29] All guidelines also highlight the association of PD with decreased quality of life and psychological health with a significant number of patients experiencing depression.

The natural history of the disease is notable for an active and stable phase.[30] All guidelines emphasize that curvature worsens in nearly half of all patients during the active phase and improves in < 10–15% of patients. In contrast, pain improves or resolves in the majority of patients. The active phase is characterized by variable penile pain with other symptoms such as penile induration, progressive deformity, or ED. There is no firmly agreed-upon timeframe that constitutes the active phase of PD, and there is both agreement and discrepancy amongst the guidelines pertaining to the definition of stable-phase PD. This is highly relevant for those patients who will undergo surgery, as there is universal agreement that all patients must be in the stable-phase prior to surgical straightening. Specifically, there is consensus that penile deformity must be unchanged for a minimum of three (to six) months. In contrast, there is discrepancy regarding the number of months

since symptom onset that defines stable disease, ranging from six-months (CUA, ISSM) to greater than 12-months (AUA).[1, 26, 28]

Evaluation [Table 1]

A common thread pertaining specifically to surgical treatment amongst the guidelines is the emphasis on expert care. The AUA states that only *experienced clinicians* should evaluate and treat PD.[1] CUA also emphasizes the appropriateness of referral to *subspecialized physicians particularly for surgical management*[26] Specifically citing the complexity of grafting surgeries, ISSM again emphasizes that these should be performed by experts.[28]

There is a notable lack of evidence regarding the workup for PD, and therefore recommendations are largely based on clinical consensus. Based on expert opinion, the AUA guideline panel recommends that clinicians should evaluate and treat PD only if they possess the experience and tools to provide appropriate diagnostic and therapeutic care.[1] A careful history and physical examination is mandated and may be all that is needed to make the diagnosis based on expert opinion from the AUA, CUA, and ISSM panels.[1, 26, 28] Each guideline highlights slightly disparate aspects of history taking, but all emphasize the importance of defining the degree of deformity and ED. Both the international index of erectile function (IIEF) and Peyronie's Disease Questionnaire (PDQ) are discussed based on their potential utility for defining symptom severity and treatment-related outcomes.[17, 21] No guideline mandates the routine use of these questionnaires, although the ISSM guideline panel explicitly emphasizes the PDQ to establish baseline data and monitor treatment outcomes.[28] All guideline panels similarly emphasize that a routine physical exam of the genitalia is mandatory in addition to history to establish the diagnosis.

According to the AUA guideline panel, no further treatment is warranted if the patient selects observation or non-invasive treatments.[1] In contrast, the EAU guideline states that objective curvature assessment is a mandatory component of the evaluation.[29] If treatment is desired, particularly invasive-treatments, further evaluation is recommended. There is complete concordance amongst guideline panels regarding in-office intracavernosal injection (ICI) with an erectogenic agent and estimation of penile angulation with a goniometer as the gold-standard for curvature assessment. The CUA endorses the use of an adequate home photograph with protractor-estimate of penile angulation as an alternative (less accurate) approach to evaluate curvature.[28] Prior to the 2020 update, the EAU penile curvature guideline allowed for home-photography.[31] The new EAU penile curvature guideline emphasizes the importance of evaluation with in-office ICI due to superiority over alternative methods of assessment, albeit based on expert opinion and with a "weak" data recommendation.[29] The AUA and ISSM guideline panels recommend ICI, but hedge by suggesting that home photography may be "sufficient" in some cases.[1, 28]

Penile ultrasound (PU) with or without Doppler (PDDU) is an adjunctive test used to characterize penile plaque and penile hemodynamics. PDDU is recommended by EAU guidelines only for the evaluation of ED, and the panel explicitly recommends against PU to characterize the penile plaque based on the weak level of evidence to support any change in diagnosis or treatment outcomes.[29] In contrast, AUA, CUA, and ISSM guideline panels support PD/PDDU as optional to evaluate plaque characteristics and penile

hemodynamics.[126, 28] Other imaging modalities including MRI, CT, and plain-film XRAY are discouraged by the CUA, EAU, and ISSM guideline panels given their lack of proven efficacy, expense, and radiation exposure.[26, 28]

Penile biothesiometry is a non-invasive test used to provide objective sensory information. However, the utility of this testing in the context of the initial PD evaluation is unproven.[32, 33] The AUA and ISSM guideline panels discuss the potential utility of biothesiometry in select patients who report diminished penile sensation. This testing may also establish baseline objective penile sensation with which to compare pre- and post-treatment.[33] Biothesiometry is not discussed by the EAU and CUA guideline panels.

Psychological Assessment

Negative psychosocial consequences with long-lasting effects are routinely encountered in men with PD.[10] These concerns are acknowledged by all guideline panels with emphasis placed on assessing psychological burden through subjective and objective measures, including the PDQ which has a specific domain pertaining to symptom bother.[1, 26, 28, 29] In the context of the guideline discussions, panels state that clinicians should consider placing a referral for consultation with a mental health professional if significant bother is identified. However, to date there are no specific guideline statements pertaining to mental health assessment and referral.

Treatment

All guideline panels explicitly iterate the importance of shared decision making as it pertains to treatment selection for Peyronie's disease. The treating physician must inform patients on potential risks, benefits, and treatment alternatives during the initial consultation and subsequent interactions. No single treatment modality is considered the standard of care, and given the benign nature observation alone is an appropriate treatment decision when made by the adequately informed patient. Treatment algorithms are included within the AUA, CUA, and EAU guidelines to assist clinicians with diagnosis and treatment options.[1, 26, 29]

Non-surgical [Table 2]

i. **Oral therapy—**Active treatment approaches are differentiated based on levels of invasiveness. There is consensus amongst guideline panels that oral therapies lack supportive evidence. AUA, CUA, and EAU panels recommend NSAIDs as first line therapy for pain in the acute phase, which is the defining feature for many patients.[1, 26, 29] CUA and EAU panels also discuss the potential role for phosphodiesterase-5 inhibitors (PDE5-I) such as tadalafil to optimize concurrent ED which is common in men with PD, noting there is also limited animal and human data regarding potential benefits with respect to fibrosis.[26, 29] The AUA, CUA, and EAU guideline panels recommend against oral therapy with vitamin E (+/− L-carnitine), tamoxifen, procarbazine, and omega-3 fatty acids due to a clear lack of efficacy.[1, 26, 29] The EAU panel recommends against potassium para-aminobenzoate (POTABA), pentoxifylline, and colchicine, whereas the AUA and CUA guideline panels consider these agents as *potential options,* along with co-enzyme Q10, when used as monotherapy or in combination with other treatment modalities (while still acknowledging the clear lack of sufficient evidence with respect to treatment efficacy). The ISSM guideline

does not recommend any oral therapy as primary treatment due to the lack of proven benefit in rigorous clinical studies to date.[28]

ii. Topical therapy—All guideline panels point to the lack of sufficient evidence to support topical therapies such as verapamil or H-100 (nicardipine, superoxide dismutase, and emu oil).[34] Electromotive drug therapy (iontophoresis) is not recommended by the AUA, CUA, and EAU guideline panels based on lack of sufficient evidence and burden of administration.[1, 26, 29] Using a slightly different take, the ISSM guideline panel underscores the lack of proven benefit and suggests that the decrease in curvature seen in some series may be due to the energy delivered to the tissue.[28]

iii. Extracorporeal shockwave therapy and Radiation Therapy—There is general agreement that extracorporeal shockwave therapy (ESWT) may be offered for pain, but not curvature correction. The AUA and CUA emphasize the low utility given that the natural progression of PD results in pain resolution for most patients.[1, 26] Radiation is not recommended by the AUA and CUA guidelines given potential associated risks which outweigh any proven benefits. This is not addressed by the ISSM or EAU.

iii. Penile traction therapy (and vacuum erection device)—The EAU guideline states that penile traction therapy (PTT) or vacuum erection devices may be used as monotherapy or in combination with other treatments to reduce penile deformity.{Salonia A., 2020 #22} This is based on multiple small studies that that have demonstrated efficacy for both curvature and penile length with a mild side effect profile. However, this recommendation is considered “weak” due to the lack of robust data to date. The CUA also recommends PTT but emphasizes the lack of defined treatment protocols including type of device and duration of use.[26] The AUA guideline panel suggests that mechanical therapies including PTT and VED are “possibly promising”, but further replication of the available study data is required.[1] This is line with recommendations by the ISSM guideline group as well.[28]

iv. Intralesional injections—Recommendations regarding intralesional injection therapy differ somewhat amongst the guideline panels. Multiple agents have been studied over the past several decades including hyaluronic acid, botulinum toxin-A, corticosteroids, verapamil, interferon-alpha 2B (IFN), and intralesional collagenase clostridium histolyticum (CCH). The latter has received national regulatory approval in the USA and was also available, until recently, in Canada and the European Union (currently CCH is no longer available in Canada or the European Union).[35]

There is considerable agreement regarding the lack of proven efficacy with corticosteroids, hyaluronic acid, and botulinum-toxin A amongst the guideline panels. Corticosteroids are specifically recommended against by the CUA and EAU panels, whereas the AUA and ISSM guidelines do not make specific recommendations but cite significant limitations in the available literature. The EAU, AUA, and CUA also emphasize the lack of robust evidence to support hyaluronic acid and botulinum toxin therapy for PD.[1, 28, 29]

Intralesional verapamil is a calcium-channel blocker that is proposed to modulate extraceullar matrix proteins resulting in beneficial therapeutic effects in men with PD.[36] The AUA guideline states that intralesional verapamil may be offered to patients, but emphasizes that the supporting evidence is somewhat contradictory and overall weak with an unclear overall balance between benefits and risks/burdens.[1] However, the side effects are generally mild and short-lived, and overall the treatment tends to be well-tolerated. Also, some authors have reported improvements in penile pain albeit in the absence of a control group.[36] A similar stance is described within the ISSM guideline.[28] The CUA considers verapamil to be a second line intralesional therapy (along with IFN), and notes that injection protocols (volume, frequency, concentration, treatment duration) likely influence outcomes.[26] The EAU guideline now actually recommends against intralesional calcium channel blockers including verapamil and nicardipine, citing the lack of proven efficacy.[29]

IFN is another intralesional therapy that modulates fibroblast proliferation leading to a change in extracellular matrix deposition and collagen production.[37] All four guidelines support intralesional IFN due to the potential modest benefits seen in the published literature including results from a multi-center, randomized, placebo-controlled trial by Hellstrom et al. in 2006.[38] It is noteworthy that, while considered second line for intralesional therapy according to the CUA guideline panel, IFN is rarely used in Canada owing to cost and potential adverse events such as sinusitis and flu-like symptoms.[26] These same potential side-effects are emphasized by the AUA, ISSM, and EAU guidelines, but are categorized as mild by these panels. Treatment inclusion criteria suggested by the AUA and CUA guidelines include non-calcified plaques with >30-degrees of curvature.[1, 26] The AUA guideline panel further suggests that the providers must keep the relatively moderate average curvature reduction of 13.5-degrees compared with 9-degree in placebo groups in mind.[1] Other potential improvements include penile pain and vascular hemodynamics, and these are again emphasized by all guideline panels.

Intralesional CCH is supported by all guidelines based on robust data from two-separate double-blind, randomized, placebo-controlled trials originally published in 2013.[19] Since that time, multiple clinical studies have shown similarly favorable results.[39] The AUA guideline states that clinicians may administer CCH for patients with stable-phase PD, penile curvature between 30 and 90 degrees, and adequate erectile function.[1] The EAU makes similar recommendations, but states that curvature should be dorsal or lateral.[29] The CUA and ISSM guideline panels consider isolated hourglass deformity and severe plaque calcification as exclusion criteria for CCH.[26, 28] Specific recommendations regarding CCH in the acute phase, ventral curvature, hourglass deformity with hinge-effect, and protocol modifications are lacking due to the absence of robust supportive evidence, but are not overtly recommended against in any published PD guideline. Finally, all panels recommend thorough counseling regarding potential side effects such as penile ecchymosis, swelling, hematoma, pain, and corporal rupture as emphasized by the AUA PD guideline statement #9.[1]

Surgical

Surgical treatment for PD includes penile plication, plaque incision or partial excision and grafting, and penile prosthesis placement with concurrent straightening maneuvers as indicated. Surgery is favored with failure of conservative management, significant deformity precluding intercourse, or patient preference. The aim is to correct penile curvature rather than pain. All guideline panels state that surgery should only be offered to patients with stable disease. They generally agree that penile curvature should therefore be stable for at least 3 months, but the ISSM panel suggests that patients should have stable PD symptoms for at least 6 months prior to surgery as compared to the AUA which indicates symptom duration of at least 12 months with 3–6 months of symptom stability.[1, 28] This lack of consensus underscores the heterogeneity in patient populations that is routinely seen within the urology literature, and supports the need for a more standardized definition to ensure consistent results reporting with subsequent intervention studies.

Levine and Lenting were one of the first groups to describe their surgical algorithm for Peyronie's Disease based on curvature severity, presence of indentation/hourglass with associated hinge-effect, and baseline erectile function.[40] Subsequent work has supported this type of objective approach to optimize postoperative outcomes.[41– 43] Specific guideline recommendations pertaining to surgical approach are left somewhat vague, providing leeway for the surgeon to offer whatever approach she/he feels is optimal. The CUA, EAU, and ISSM guideline panels suggest that plaque incision with grafting be reserved for men with more severe penile deformity.[26, 28, 29] These panels use descriptions such as curvature that is "reasonably correctable", "non-severe", and "minimal to moderate", respectively, to define that which may be more amenable to plication techniques. In contrast, the AUA guideline panel does not make specific recommendations regarding the decision to pursue plication versus grafting.[1]

Based on current guideline iterations there are no formal recommendations given in favor of specific surgical techniques for plication or tunical incision/partial excision with grafting. This is due to the lack of available evidence comparing outcomes within and amongst these techniques. The EAU states that a de-gloving incision is considered standard, but other modifications such as a ventral incision have been described.[29] They also emphasize that non-absorbable or slowly absorbable sutures should be used to minimize the risk for curvature recurrence during plication procedures. With respect to grafting procedures, there is no specific graft material favored by any one society. The CUA, EAU, and ISSM panels recommend strongly against synthetic grafts as they have been associated with adverse outcomes including persistent/recurrent fibrosis and infection.[26, 28, 29] Interestingly, the CUA highlights the utility of PTT post-plication to optimize outcomes including length, albeit with limited studies regarding efficacy at this time.[26] ISSM also highlights traction in combination with PDE-5i as an option for penile rehabilitation.[28]

There seems to be consensus amongst the panels that inflatable penile prosthesis models are generally preferred, although the EAU guideline cites similar satisfaction rates with malleable prosthesis models as well.[29] The guideline panels all state that penile prosthesis should be considered for men with medication-refractory ED and PD who desire definitive management with additional maneuvers employed as necessary to optimize penile

straightening. One of the original algorithms regarding penile prosthesis placement with concurrent straightening maneuvers for combined PD/ED was published by Levine and Dimitrou in 2000.[44] ISSM and the recent EAU guidelines both outline similar algorithms for the adjunctive procedures often employed with IPP placement, based on this and other earlier publications.[28, 29]{Levine, 2000 #33} For residual curvature > 30 degrees after prosthesis placement, manual modeling is recommended as first line. If the curve remains >30 degrees after modeling, penile plication or plaque releasing incisión with/without grafting/coverage can be employed. Per the ISSM guideline, grafting over the defect is recommended if a defect >2 cm results.[28, 44] Sliding techniques or other "length-restoration" approaches to increase penile length are to be used with caution per the EAU, given the risk of serious side effects, and should be offered only by highly experienced surgeons.[29]

A discussion regarding potential side effects prior to surgery is mandated by all guideline panels. Specific risks include perceived or actual penile shortening, ED, penile sensation changes, and persistent or recurrent curvature. CUA and ISSM panels also highlight possible orgasm and ejaculation changes with surgical treatment. The EAU, CUA, and ISSM panels specifically emphasize the concept of a "functionally" straight penis (i.e. within 20º of straight as opposed to "arrow" straight).[26, 28, 29, 45] ED and sensory loss are less common with plication, particularly when neurovascular bundle elevation is not required. Risks specifically pertaining to penile prosthesis placement include device infection, mechanical malfunction, and urethral perforation (if modeling is performed).[1, 26, 28, 29]

Discussion:

There are inherent challenges pertaining to the evaluation and treatment of men with PD.[21] Moreover, the bulk of the available literature suffers from methodologic and statistical flaws with poor study design and inadequate power to assess treatment effect. Much of the data that we use to counsel our patients is based on very low-level evidence such as retrospective, single-surgeon or single-center cohorts with limited follow-up and absent controls. In this context, the four separate clinical guidelines reviewed herein provide readers with a summary of the available evidence, with the goal of providing a framework upon which to build treatment plans for patients suffering from PD.

Upon thorough review of the guidelines, we identified a high degree of concordance on many topics. The following statements highlight areas of consensus amongst the major societies, but it should be noted that there is a paucity of rigorous, multi-center, and long term outcomes data comparing treatment strategies.

- History and physical examination is mandatory and can be used to diagnose PD.
- Intracavernosal injection is the gold standard to evaluate penile deformity, particularly prior to invasive intervention.
- Careful counseling with shared decisión making is required at the onset of treatment, and patients should be aware of limitations with the available data pertaining to treatment options.

- Extracorporeal shock wave therapy can be used to treat penile pain associated with PD, but should not be used to address penile deformity such as curvature or plaque size.
- Intralesional injections may be offered to patients who desire non-surgical treatment.
- Surgery should only be offered to patients who are in the stable or chronic phase of PD.
- Plication and incision and/or grafting surgery is reserved for patients with preserved erectile function, whereas penile prosthesis implantation is the optimal surgical option for PD patients with erectile dysfunction unresponsive to pharmacotherapy and/or VED.

Further research into PD evaluation and treatment is needed. Delineation of PD pathophysiology has the opportunity to direct novel treatments targeted towards early intervention of causal mechanisms.[1] Penile deformity assessment is marred by high inter and intra-user variability. Patient recall and photography (home or in-office photographs) are more convenient than performing an objective curvature assessment, but they lack objective information on penile girth deformities and erection firmness.[46–48] This may lead to inaccurate curvature estimation in many instances. When one considers that many of the treatments we offer patients have an average curvature improvement of 10–20 degrees, even small margins of error may have significant consequences.[21] New and innovative technologies, such as three-dimensional photography and even a cell-phone based photograph application have the potential to revolutionize our assessments.[49, 50] These tools seem even more relevant in the current era of the coronavirus epidemic where telemedicine-based platforms are gaining popularity.[51]

As noted by all of the guideline panels, PD carries a significant psychological burden for the majority of patients and even their partners. Prior to the development of the PDQ, we had very few objective tools with which to assess the psychosocial impact of PD symptoms and treatments. The PDQ is considered an adjunctive evaluation tool by the CUA and ISSM, and the EAU now recommends this tool during the initial assessment and subsequent follow-up to determine treatment efficacy beyond simple objective measurements.[26, 28, 29] Yet, there are limitations with this questionnaire including the requirement that patients have engaged in penetrative sexual intercourse within the preceding 3 months.[21] Other questionnaires such as the IIEF and the erection harness scale provide objective information on erectile function, but have not been validated in the PD population. Objective and standardized measures pertaining to the perceptions of sexual partners and specific investigations into outcomes in non-cis gendered and/or non-heterosexual men and their partners are also needed.[15, 52] Developing these and other novel questionnaires will enhance our assessment toolbox and expand our definition of treatment success.

Conclusions:

Four different clinical guidelines have been published to streamline the evaluation and management of PD. Generally agreed upon principles for the clinical evaluation include

appropriate clinician expertise, a thorough history and physical examination, and use of objective curvature assessment prior to invasive therapy. With respect to definitive treatment, consensus supports that oral medications are generally efficacious, intralesional injections are an appropriate noninvasive treatment option, and surgery should be reserved for patients in the stable phase of disease (although this definition somewhat varies). In addition, penile prosthesis is the best surgical option for patients with medication refractory ED. Ongoing rigorous basic science and outcomes research is needed to guide emerging novel treatments as well as direct patient selection for surgical techniques.

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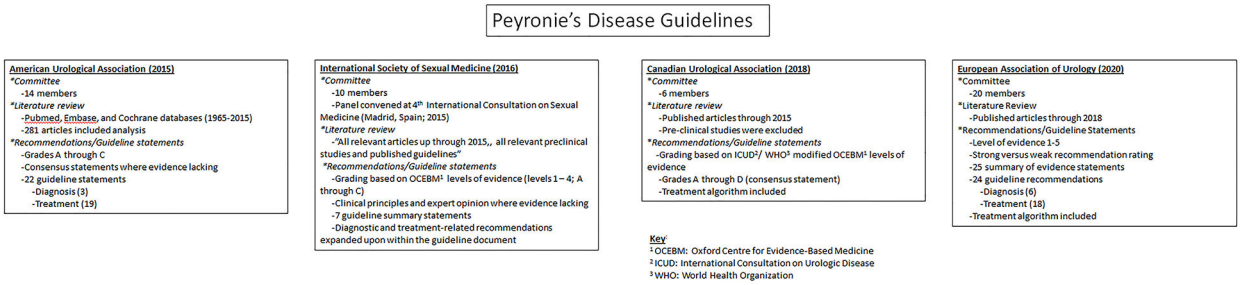

Figure 1.
Peyronie's Disease Guidelines OverView

Table 1.

Peyronie's Disease Evaluation

	AUA (2015)	CUA (2018)	EAU (2020)	ISSM (2016)
Definition of "stable" phase PD	- Symptom duration ≥ 12-months; stable PD symptoms for 3–6 months *(Clinical principle)*	- Symptom duration > 6–12 months; stable PD symptoms for 3–6 months	- Symptom duration > 9–12 months; stable PD symptoms for 3–6 months *(Level 2b; Strong)*	-Symptom duration >6–12 months; stable PD symptoms for > 3-months *(Expert opinion)*
History and physical examination	Recommended *(Clinical principle)*	Recommended *(Level 4; Grade C)*	Recommended *(Strong)*	Recommended *(Clinical principle)*
Questionnaires	Not addressed	May consider -IIEF[a] -PDQ[b] *(Level 3; Grade C)*	May consider -IIEF[a] -PDQ[b] *(Weak)*	Recommended -PDQ[b] *(Level 4; Grade B)*
Mental health referral	May consider	May consider	May consider	May Consider
Home photograph (full erection)	May consider	May consider	May consider -Should not replace curve assessment with ICI	May Consider -Could be sufficient for baseline and monitoring if no invasive tx is undertaken
ICI	Recommended prior to invasive intervention *(Expert opinion)*	Recommended *(Level 4; Grade C)*	Recommended *(Level 4; Weak)*	Recommended prior to invasive intervention *(Expert opinion)*
Doppler US	May consider *(Expert opinion)*	May consider *(Level 4; Grade C)*	May consider -Assessment of penile hemodynamics and vascular anatomy -NOT recommended for plaque size estimation *(Level2a/3; Weak)*	May consider *(Level 3; Grade C)*
Biothesiometry	May consider	Not addressed	Not addressed	May consider
MRI	Not addressed	Recommended against	Recommended against	Recommended against *(Level 3; Grade C)*
CT	Not addressed	Recommended against	Recommended against	Recommended against *(Level 3; Grade C)*
XRAY	Not addressed	Recommended against	Not addressed	Recommended against *(Level 3; Grade C)*

[a] International Index of Erectile Function

[b] Peyronie's Disease Questionnaire

[c] Recommended to evaluate erectile dysfunction but NOT for plaque measurement

Table 2.

Non-surgical Treatment Options for Peyronie's Disease

	AUA (2015)	CUA (2018)	EAU (2020)	ISSM (2016)
NSAIDS	Recommended -For pain in active phase *(Expert opinion)*	Recommended -For pain in active phase	May consider -For active-phase pain *(Level 5; Strong)*	Not addressed
Vitamin E	Recommended against *(Grade B)*	Recommended against	Recommended against *(Grade 3c; Strong)*	Recommended against *(Grade B; Level 2)*
Tamoxifen	Recommended against *(Grade C)*	Recommended against	Recommended against *(Grade 3c; Strong)*	Recommended against *(Grade B; Level 2)*
Procarbazine	Recommended against *(Grade C)*	Recommended against	Recommended against *(Grade 3c; Strong)*	Not addressed
Omega-3 fatty acids	Recommended against *(Grade B)*	Not addressed	Recommended against *(Grade 3c; Strong)*	Not addressed
Vitamin E + L-carnitine	Recommended against *(Grade B)*	Recommended against	Recommended against *(Grade 3c; Strong)*	Recommended against *(Grade B; Level 2)*
Potassium para-aminobenzoate	Unclear benefits (no recommendation)	May consider *(Level 3; Grade C)*	Recommended against *(Grade 3c; Strong)*	Recommended against
Colchicine	Unclear benefits (no recommendation)	May consider *(Level 3; Grade C)*	Recommended against *(Strong)*	Recommended against *(Grade B; Level 2)*
Pentoxifylline	Unclear benefits (no recommendation)	May consider *(Level 3; Grade C)*	Recommended against *(Grade 3c; Strong)*	Recommended against *(Grade B; Level 2)*
Co-enzyme Q10	Unclear benefits (no recommendation)	May consider *(Level 3; Grade C)*	Not addressed	Not addressed
PDE-5 inhibitors	Not addressed	May consider	May consider -To treat concomitant ED -To optimize penetration if deformity makes penetration intercourse difficult *(Weak)*	Recommended against -To benefit penile deformity with PD -ED treatment not addressed *(Grade B; Level 2)*
Electromotive therapy + topical Verapamil	Recommended against (*Grade C)*	Recommended against	Recommended against *(Level 3c)*	Recommended against *(Level 3; Grade B)*
Topical therapy (monotherapy)	Unclear benefits (no recommendation)	Unclear benefits with topical verapamil (no recommendation) *(Level 4; Grade C)*	Recommended against (Level 3c)	Not addressed
Penile traction	Unclear benefits (no recommendation)	May consider *(Level 4; Grade C)*	May consider *(Level 3c; Weak)*	May consider *(Level 3; Grade C)*
Extracorporeal shock wave therapy	May consider -For pain only -Do not offer for plaque size or penile curvature *(Grade B)*	May consider -For pain only -Do not offer for plaque size or penile curvature *(Level 2, Grade C)*	May consider -For pain only -Do not offer for plaque size or penile curvature *[Level 2b; Weak (pain)/ Strong (plaque/curve)]*	May consider -For penile pain -Panel experts suggest potential benefit on symptom stabilization (does NOT correct deformity) *(Level 3; Grade B)*
Radiation therapy	Recommended against *(Grade C)*	Recommended against	Not addressed	Not addressed
Intralesional therapy				
CCH	May consider *(Grade B)*	May consider *(Level 2; Grade B)*	May consider *(Level 1b; Strong)*	May consider *(Level 2; Grade B)*
Inclusion criteria (Optimal patient characteristics)	−30–90° curve -"Stable" symptoms -Intact erectile function	−30–90° curve -No isolated hourglass -Non-calcified plaque	− >30° curve -Dorsal or later curve -Patients who desire non-	−30–90° curve -No isolated hourglass -Non-calcified plaque

	AUA (2015)	CUA (2018)	EAU (2020)	ISSM (2016)
	with or without medical therapy	-“Stable” symptoms -Intact erectile function with or without medical therapy	surgical treatment -“Active” or “stable” phase	-Plaque NOT located at penile base -“Stable” symptoms -Intact erectile function with or without medical therapy
IFN	May consider *(Grade C)*	May consider *(Level 2; Grade B)*	May consider *(Level 2b; Strong)*	May consider *(Level 2; Grade B)*
Optimal patient characteristics	- > 30° curve -“Stable” symptoms -Non-calcified plaque	- > 30° curve -Non-calcified plaque	- > 30° curve -Dorsal or lateral curve -“Stable” phase	Not addressed
Verapamil	May consider *(Grade C)*	May consider *(Level 2; Grade B)*	Recommended against *(Level 1b)*	May consider *(Level 3; Grade C)*
Optimal patient characteristics	Not addressed	Not addressed	-N/A	Not addressed
Corticosteroids	Not addressed	Recommended against *(Grade C)*	Recommended against *(Level 3c; Strong)*	Recommended against
Hyaluronic acid	Not addressed	Unclear benefits (no recommendation)	Recommended against *(Level 3c)*	Not addressed
Botulinum toxin	Not addressed	Unclear benefits (no recommendation)	Recommended against *(Level 3c)*	Not addressed
Combination therapies	Unclear benefits (no recommendation)	Not addressed	May consider *(Level 3c; Weak)*	May consider

Table 3.

Criteria for Surgical Management Options of Stable Peyronie's Disease

	AUA (2015)	CUA (2018)	EAU (2020)	ISSM (2016)
Plication	-Stable PD -Adequate erectile rigidity with or without pharmacotherapy or VED *(Grade C)*	-Stable PD -Adequate erections with or without pharmacotherapy -Adequate penile length -Curve that is "reasonably correctable with this approach" -Minimal/absent hourglass + hinge *(Level 3; Grade C)*	-Stable PD -Adequate erections with or without pharmacotherapy -Adequate penile length -Absence of complex deformity (hourglass, hinge) -"Non-severe" curvature *(Level 3; Weak)*	-Stable PD- -Adequate erections with or without pharmacotherapy -Adequate penile length -Minimal to moderate curvature -Absence of hourglass causing hinge *(Level 3; Grade B)*
Preferred plication technique	Not specifically addressed	Dependent on surgeon and patient factors	-Dependent on surgeon and patient preference -No procedure with proven superiority	-No surgical procedure with proven superiority
Incision or excision and grafting	-Stable PD -Adequate erectile rigidity with or without pharmacotherapy or VED *(Grade C)*	-Stable PD -Adequate erections with or without pharmacotherapy -Short penile length -Severe curvature > 60° -Large penile plaques -Complex indentation or hourglass *(Level 3; Grade C)*	-Stable PD -Adequate erections with or without pharmacotherapy -Significant penile shortening -Severe penile curvature (>60°commonly cited but, per the guideline panel experts there is no unanimous consensus to support this threshold) -Complex deformities (hourglass, hinge) *(Level 3; Weak)*	-Stable PD -"Good" erectile function -Significant curvature and/or Indentation/hourglass deformity (with or without -Concerns regarding further penile length loss *(Level 3; Grade B)*
Preferred graft material	Not addressed	-No preferred graft -Recommend against synthetic grafts *(Level 3; Grade C)*	-No preferred graft material -Recommend against synthetic grafts *(Strong)*	-No ideal/preferred graft -Synthetic grafts not recommended
Penile prosthesis with adjunctive procedures*	-Stable PD -ED and/or penile deformity that impairs coitus (despite pharmacotherapy or VED) *(Grade C)*	-Stable PD -ED non-responsive to pharmacotherapy -Severe deformity refractory to non-surgical management -failed plication or grafting -Profound penile instability (buckling or hinge) *(Level 3; Grade C)*	-Stable PD -ED unresponsive to pharmacotherapy *(Level 2a; Strong)*	-Stable PD -ED with inadequate response to pharmacotherapy or VED -Complex deformity *(Level 3; Grade B)*
Preferred prosthesis	-Inflatable prosthesis is preferred *(Expert opinion)*	-Inflatable prosthesis is preferred *(Level 3; Grade C)*	-Inflatable prosthesis classically considered more effective -Malleable with similar satisfaction rates -Patient and surgeon preference should determine device type and model	-Inflatable penile prosthesis associated with higher satisfaction and lower persistent curvature compared with malleable -Similar outcomes with commercially available inflatable prosthesis models

* Adjunctive procedures may include manual modeling, plication, incision, or grafting