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Review

History of Peyronie's disease: from early descriptions to modern treatments

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Abstract

Introduction: Peyronie's disease (PD) is a fibroproliferative disorder of the tunica albuginea characterized by localized plaque formation, penile curvature, and erectile dysfunction, most commonly affecting men between 40 and 70 years of age. Although François Gigot de La Peyronie is credited with the first formal description of the disease in 1743, depictions of penile curvature predate his description by millennia.

Objectives: This review aims to provide a comprehensive understanding of the historical and contemporary evolution of therapeutic strategies for PD, highlighting the shift from anecdotal remedies to evidence-based approaches.

Methods: PubMed, Cochrane, and Embase databases were searched without restrictions on publication date, using keywords related to PD and its therapies. Key interventions, including oral and topical agents, intralesional injections, penile traction therapy (PTT), and surgical techniques, were analyzed in the context of clinical trial data and guideline recommendations.

Results: Early therapeutic approaches focused on oral and topical agents, which failed to demonstrate consistent efficacy in randomized trials. Intralesional injection (ILI) therapy has emerged as a leading option for nonsurgical management, with collagenase *Clostridium histolyticum* (CCH) as the standard treatment supported by robust evidence of significant improvements in penile curvature. PTT has undergone considerable refinement, with second-generation devices yielding excellent outcomes, particularly when combined with CCH. Surgical intervention remains the gold standard for definitive treatment of severe or complex deformities. Technical modifications have developed, including the use of biologic grafts, inflatable prosthesis placement with manual modeling, and graftless techniques such as tunica expansion and auxetics.

Conclusion: A review of the historical progression of PD management demonstrates the shift from anecdotal claims of treatment efficacy to evidence-based practice. Current guidelines recommend ILI and PTT as first-line nonsurgical management, with surgery providing exceptional outcomes. Future progress aims to gain a greater molecular understanding of fibrosis and tissue remodeling to foster targeted therapies.

Keywords: Peyronie's disease; history; treatment; nonsurgical therapy.

Introduction

Fibroproliferative (FP) diseases are common age-related pathologies and surprisingly account for more than 40% of mortalities in industrialized nations.[1] FP wound-healing disorders can affect nearly all organs and tissues of the body and manifest as well-known conditions, such as lung fibrosis, liver cirrhosis, atherosclerosis, keloids, renal diseases, and systemic sclerosis. While these conditions show similar basic pathophysiologies, they are, unfortunately, rarely studied collectively.

Peyronie's disease (PD) is a localized FP connective tissue disorder affecting the tunica albuginea (TA) of the penis, characterized by changes in collagen composition and the development of fibrotic plaques. The end results of this fibroblastic proliferation is an alteration in penile anatomy and may contribute to erectile dysfunction (ED) in 40% of affected men.[2] The TA plays a crucial role in erections, impacting penile elasticity, rigidity, compliance, and veno-occlusion.[3] Because of these physical changes and their functional consequences, PD also affects the quality of life of patients and their partners, with the majority demonstrating psychological distress.[4]

While named after Francois de La Peyronie, who described a case series of several patients with this presentation in 1743,[5] there are numerous earlier accounts of this bothersome penile deformity.[6] Notably, cave paintings located in the middle of America along the Colorado river, dated over 2000 years ago, document significant penile curvature in a hunter (Figure 1).

While these historical observations underscore the long-standing occurrence of PD, modern clinical data have

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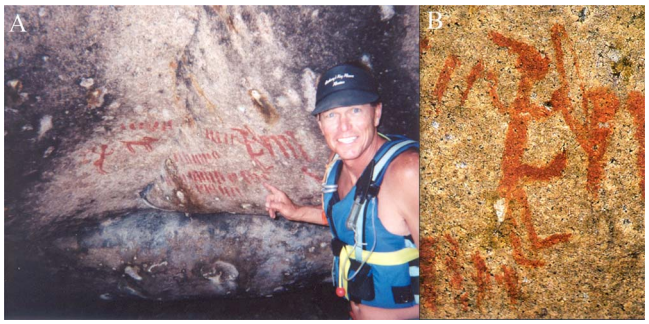

Figure 1. Depiction of penile curvature in an ancient cave painting. (A) Cave painting of a hunter. (B) Magnified image of a hunter. *Photo credit: Dennis Venable, MD. Published with permission.*

helped define the typical patient population affected by this condition.

PD usually presents in males between ages 40 and 70 years (mean 57 years); studies report incidence rates ranging from 0.39% to 20%, with a general consensus that 3%-4% of adult men suffer from PD.[7]

There are a myriad of proposed theories regarding the origin of PD; however, most authorities support the concept of repetitive microvascular trauma inciting a low-level autoimmune-inflammation response.[8] The release of cytokines activates fibroblast conversion to myofibroblasts and induces collagen production, fibrosis, and the formation of the characteristic PD plaque. It appears that this phenomenon is a wound-healing disorder much like keloid formation, Dupuytren's contracture, and plantar fasciitis.

The most recent concepts suggest a complex interaction between resident structural tissues and immune cells in the development of PD. The accumulation of senescent cells during injury repair overwhelms the clearing mechanism and results in a pathological fibrotic-tissue response. Novel agents that target cytotoxic T-lymphocyte-associated protein 4 have demonstrated improved cellular regeneration and diminished fibrosis in specialized murine models of idiopathic pulmonary fibrosis.[9]

The major aim of this communication is to give a historical perspective of this well-known urological entity. The moniker "Peyronie's disease" derives from a venerated French surgeon who elevated surgeons from the cast of barbers and bloodletters. Numerous oral and topical agents have been advocated over the centuries. Unfortunately, many of these reported successes were primarily anecdotal, involving small sample sizes, short study durations, and a lack of placebo-controlled arms. More recent evidence supports intralesional delivery of specified agents with ancillary penile stretching. Surgical options range from plication, incision/excision with grafting, and penile prosthesis (PP) implantation, with adjunctive procedures as necessary. PD has a colorful past as documented. Knowing the past pitfalls and successes will guide future investigation, innovation, and therapeutic success.

Methods

PubMed, Cochrane, and Embase databases were searched without restrictions on publication date, using vocabulary and keywords related to PD and its therapies (eg, oral, topical, intralesional injection, collagenase *Clostridium histolyticum*

Figure 2. Portrait of François Gigot de La Peyronie. Hyacinthe Rigaud. François Gigot de La Peyronie, Faculté de médecine de Paris. Paris Descartes University. [Public domain.]

[CCH], penile traction therapy [PTT], surgery, penile grafting/incising/excising, prosthesis, modeling, tunica expansion, auxetics, etc.). Contemporary clinical guidelines from major societies, such as the American Urological Association (AUA), Sexual Medicine Society of North America (SMSNA), International Society for Sexual Medicine (ISSM), European Association of Urology (EAU), and European Society for Sexual Medicine (ESSM), were reviewed to provide recommendations alongside the historical chronology of PD management.

François Gigot de La Peyronie: Life, legacy, and medical contributions

François Gigot de La Peyronie (1678-1747) (Figure 2), the eponymous barber-surgeon, is credited with describing—and providing the only reported instance of—complete eradication of *induratio plastica penis* through mercurial and holy water washings.[5] Whether this seemingly miraculous cure stemmed from La Peyronie's strict Jesuit upbringing or from divine intervention remains a mystery. La Peyronie, a surname derived from the Occitan and Old French root *peyre*—meaning *stone*—was born in 1678 in Montpellier, France. His father was a "stonecutter" or lithotomist, while his mother was deeply religious, ensuring to instill this conduct into young La Peyronie. Montpellier was and is a center of education and learning on the southwestern Mediterranean coast, owing to its location near the North African caliphate academia as well as those of Spain and Italy. Montpellier became a pinnacle for medical training during the reign of King Louis XIV and his son Louis XV.[10]

La Peyronie studied philosophy and surgery as a teenager. By 1695, he had followed in his father's footsteps, earning his diploma as a barber-surgeon.[11] Within two years, he recognized a need for more training and moved to Paris to study under one of the foremost surgeons of the age, Georges Mareschal, Seigneur de Bievre. Georges Mareschal was the son

of an Irish-born barber-surgeon who had distinguished himself to the King of France during war. Mareschal started as a surgical assistant in 1677 and then became Master Surgeon in 1688. He arose to Chief Surgeon in the French court in 1692. By then, he was Attending Surgeon to Louis XIV of France, attending to him even unto his deathbed. Mareschal continued as Royal Surgeon to Louis XV. Thus, he was a worthy mentor for the young barber-surgeon from Montpellier.[12]

It is important to understand that deep animosity existed between surgeon guilds, barbers, bloodletters, and university-trained physicians during this time, with conflicts among these factions sometimes escalating to violence. After his extended training in Paris, La Peyronie returned to his hometown, where he became a lecturer in anatomy and surgery. He rose quickly to become Surgeon Major at Hotel-Dieu de Montpellier, where he subsequently founded the Royal Society of Sciences of Montpellier in 1706,[11] bringing the academic minds of all previously feuding factions together within the city.[13]

Alongside his position at Hotel-Dieu de Montpellier, he held another prestigious role, as King Louis XIV called on him to organize and command the royal military's surgical operators in response to the Calvinist revolt in 1702.[11] This role would continue under the reign of Louis XV, with La Peyronie gaining invaluable surgical experience from treating wounded soldiers and educating the next generation of surgeons for France. It is speculated that during this time, he described his technique of a *defunctioning* bowel in patients with a devitalized, obstructed, or gangrenous bowel. The technique involved excision of the devitalized segment and subsequent "back-to-back" enterostomy, with sutures placed within adjacent loops of mesentery to promote fistulation. La Peyronie dubbed this technique *defunctioning enterostomy,* which he did not officially report until 1743, when he described two civilian cases.[14]

In 1715, he returned to Paris to rejoin his mentor, Mareschal. Prior to their most notable collaboration in 1731, barber-surgeons struggled to escape their relatively nonacademic heritage. Together with others, Mareschal and La Peyronie petitioned for a law banning barbers from practicing surgery, leading to the formation of the Académie Royale de Chirurgie (Royal Surgical Society of France) in 1731. This institution placed physicians and surgeons on the same academic footing for the first time. Upon Mareschal's death in 1736, La Peyronie was appointed Royal Surgeon to Louis XV. Some of his more notable patients included Peter the Great of Russia and Infanta Maria Teresa Rafaela of Spain.[11-13]

Although La Peyronie was granted credit for the discovery of the disease *induratio plastica penis* (now known as PD), he was not the first to describe this malady, which had been noted centuries earlier under various names across the continent. Some of the earliest documented observations came from Gabriele Falloppia (1523-1562), the Chairman of Anatomy and Surgery at University of Padua, who was best known for his description of the middle ear bones, the ileocecal valve, and the uterine (Fallopian) tubes named after him. In 1551, he wrote, "Painless ganglia, or glands as they are called, form in the nerves and their coverings, which cause the penis, when erect, to swell in a twisted shape like a ram's horn."[15]

Similarly, Andreas Vesalius (1514-1564), the father of modern anatomy and court surgeon to Charles V, Holy Roman Emperor, described, "a certain distinguished man who consulted you at Padua because of these nodules, … had some nodules which twisted his penis rather remarkably."[16] Giulio Cesare Aranzi (1530-1589) of the University of Bologna further noted that symptoms appeared only during an erection, when the penis became distorted and distressingly painful, with a small bean-sized tumor present.[15] Another earlier account comes from Claas Pieterzoon Tulp (Nicholaus Tulpius) (1593-1674) of Amsterdam, who is best known today as the subject of Rembrandt painting's *The Anatomy Lesson of Dr. Nicolaes Tulp*. In 1652, he wrote, "there was once a citizen of Campenzi who found, when he tried to pay court at Venus, that the middle part of his penis became bent, and he was very often forced to abandon the attempt. Treated with purges, baths, and oils. Never returned."[15]

Finally, we arrive at the description given by La Peyronie who wrote *Sur quelques obstacles qui s'opposent à l'éjaculation naturelle de la semence*[5] as a treatise on male sexual dysfunction, among other reproductive issues. He described indurations like *rosary beads* along the shaft. He recommended treatments of topical mercury and bathing in the holy waters of Bérege, reporting cures of this malady in three cases with this method. François Gigot de La Peyronie should be placed among the heroes of surgery for multiple reasons. Like all of these mentioned heroes, he was a product of other great surgeons. However, we probably owe the eponym to his relationship to royalty.

Oral and other therapies for PD: An historical overview

Oral and topical therapies as treatment for PD have existed prior to the formal naming of the disorder by La Peyronie.[5,17] Historically, nonsurgical treatment options for PD have been categorized into oral, topical, external, and intralesional approaches, with some studies assessing the potential efficacy of combination therapies.[17] Two recent review articles address the subject of medical management and nonsurgical management of PD, serving as sources of historical data on noninjection and topical therapies.[18,19] To date, only six oral agents have been evaluated in randomized clinical trials (RCTs), with most national and international guidelines either highlighting their limited efficacy or explicitly recommending against their use in PD management. These agents include vitamin E, potassium para-amino benzoate (POTABA), procarbazine, tamoxifen, colchicine, and carnitine.[18]

Oral agents

Historical descriptions

Mohede et al. identified six agents used for the treatment of PD between 1890 and 1955, including sulfur compounds, copper sulfate, salicylate and thiosinamine, arsenic, milk, and estrogens. These reports were published mostly in foreign presses, with four lacking titles and one appearing in a textbook. In 1943, Wesson reported the use of oral di-sodium phosphate as treatment for PD.[17] Since the late 1940s, more oral modalities have emerged, yet robust data on efficacious oral treatments remain lacking (Table 1).

Vitamin E (1949)

By the mid-1900s, there was an appreciable increase in the veracity of scientific validation compared with the historically accepted single-physician accounts. In 1949, the first documented use of vitamin E for treatment for PD was reported.[20] Mechanistically, vitamin E is a natural antioxidant

Table 1. Timeline of oral therapies for the treatment of Peyronie's disease.

Date	Event
Oral therapies	
1743	Mercury and mineral water
1949	Vitamin E
1959	Potassium para-aminobenzoate
1970	Procarbazine
1992	Tamoxifen
1994	Colchicine
2001	Carnitine
2006	Pentoxifylline
2011	Phosphodiesterase 5 inhibitors

by inactivating free radicals and reducing oxidative stress, which is believed to reduce collagen deposition and improve endothelial function.[18,19] A small randomized, double-blind, crossover, placebo-controlled trial involving 60 patients (only 47 completed the study) was published in 1983, in which patients randomly received either vitamin E (20 mg) or placebo 3 times daily for 3 months each. The study found no significant difference between the vitamin E and placebo groups, except for improvement in pain.[18,21] A recent systematic review analyzed four randomized studies published between 2003 and 2013.[19] The largest of these studies, involving 236 patients and published in 2007, failed to show differences between the cohorts.[19,22] The other three randomized studies—one in 2003 and two in 2013—demonstrated improvements in penile curvature, plaque size, or erectile function (EF), though the overall quality of evidence was considered moderate.[19] It is worth noting that the lead author of three of these studies, Iranian urologist Mr. Safarinejad, has had seven published articles retracted, one of which is a 2009 report on oral treatment for PD published in the *Journal of Sexual Medicine*, and this report has been excluded from this historical review.

POTABA (1959)

POTABA has been shown to stabilize serotonin-monoamine oxidase activity and directly inhibit fibroblast glycosaminoglycan secretion, contributing to its anti-inflammatory and antifibrotic effects.[18] The first reported use of POTABA for the treatment of PD was in 1959, in which 21 patients, nonrandomized, received 12 grams in 4 or 6 divided doses daily from 3 months to 2 years. Pain was relieved in all 16 patients, penile deformity resolved or improved in 14 of 17 patients, and plaques resolved or decreased in size in 16 of 21 patients.[23] A preliminary report published in 1983 described a randomized, 12-month trial of 41 men treated with POTABA compared with placebo; only improvement in pain was observed. Although the study was intended to include 64 men, the full results were never published.[18,24] In a 2005, randomized, placebo-controlled trial involving 103 men (75 included in the final results) with noncalcified plaques and without previous treatment, oral POTABA therapy administered for less than 12 months showed no significant difference in outcomes compared with placebo.[18,25]

Procarbazine (1970)

In 1970, the use of procarbazine for the treatment of PD was reported with great success, with comparable results replicated in 1971.[26,27] Procarbazine was hypothesized to inhibit the rapidly dividing fibroblasts responsible for the excess scar tissue in the TA. However, shortly after, a small case series involving 10 patients showed less than encouraging results as well as significant side effects associated with this cytotoxic medication.[27] In 1978, a randomized trial assigned 34 men to receive either procarbazine (20 mg 2 times daily) or vitamin E (20 mg 3 times daily) for 3 months. Only 67% completed the study, and vitamin E showed superior outcomes, while procarbazine demonstrated limited efficacy, thereby providing no substantial evidence to support its use.[18,28]

Tamoxifen (1992)

Tamoxifen, a nonsteroidal antiestrogen, inhibits keloid fibroblast proliferation and collagen production by decreasing the production of transforming growth factor beta, thereby affecting deposition of scar tissue.[18,19] The first report of its use in the treatment of PD appeared in a preliminary 1992 study of 36 patients treated with tamoxifen (20 mg 2 times daily) for 3 months. Eighty percent of patients reported improvement of pain, and approximately 33% noted improvement in curvature and at least a 1-cm shrinkage of plaque size.[17,29] Only one RCT, published in 1999, used the same dosage (20 mg 2 times daily for 3 months) compared to placebo. This study showed no significant differences between tamoxifen and placebo.[18,19,30]

Colchicine (1994)

Colchicine is believed to activate collagenase and decrease collagen synthesis, suggesting a potential therapeutic role in the treatment of PD.[19] In 1994, a pilot study investigated oral colchicine in 24 patients treated for 3-5 months. Plaque decreased or disappeared in 12 patients, pain was significantly relieved in 7 of 9 patients, and penile curvature improved in 7 of 19 patients.[31] An RCT published in 2004 assessed the efficacy of oral colchicine (0.5-2.5 mg) versus placebo in men with a mean disease duration of 15 months. The study failed to demonstrate any significant difference between colchicine and placebo in terms of efficacy.[18,19,32] In 2003, a single-blind study evaluated combination therapy of colchicine (1 mg 2 times daily) plus vitamin E (600 mg 2 times daily) compared with ibuprofen (200 mg 2 times daily) for 6 months in 45 patients with early-stage PD (time from onset less than 6 months), penile curvature less than 30°, and no ED. Significant improvement in pain, curvature, and plaque size occurred in the combination therapy group.[18,33]

Carnitine (2001)

Carnitine inhibits acetyl-coenzyme A and increases mitochondrial respiration and the metabolism of fatty acids and free radicals.[18,19] One small RCT in 2001 compared tamoxifen (20 mg 2 times daily) to acetyl-L-carnitine (1 g 2 times daily) for 3 months in 48 patients. However, patients in the study did not represent typical PD cases, with participants exhibiting only mild curvature and a mean disease duration of only 5 weeks. Tamoxifen was associated with more side effects compared to carnitine. Carnitine demonstrated modest improvement in penile curvature and slightly more in plaque size compared with tamoxifen.[18,19,34]

Pentoxifylline (2006)

Pentoxifylline, a xanthine derivative, is a nonspecific phosphodiesterase inhibitor with demonstrated anti-inflammatory and antifibrotic properties. Its first reported use in the treatment

of PD was in 2006, in which a single patient received pentoxifylline (400 mg 3 times daily) for 6 months. The patient showed improvement in EF, resolution of dorsal calcification, and decreased plaque size.[35]

Phosphodiesterase type 5 inhibitors (2011)

Phosphodiesterase type 5 (PDE5) inhibitors increase cyclic guanosine monophosphate levels by preventing its conversion to guanosine monophosphate, thereby prolonging the vasodilatory effects of nitric oxide. While primarily used as an effective treatment for ED, PDE5 inhibitors have shown promising potential in the management of PD. In 2011, 65 patients were given tadalafil (2.5 mg once daily) for 6 months, resulting in the resolution of septal scar tissue observed via duplex ultrasound. However, the majority of these patients did not initially present with penile curvature.[36] Subsequently, a nonblinded RCT in 2014 involved 39 patients who received either vitamin E (400 IU once daily) or sildenafil (50 mg once daily). Improvements in both penile curvature and plaque volume were reported.[37] Notably, these studies did not use the typical therapeutic doses of PDE5 inhibitors (5 mg daily for tadalafil or 100 mg for sildenafil), raising questions about a possible dose-dependent relationship in treatment efficacy. Though these results have not been further validated, they offer hope for a noninvasive and well-tolerated treatment modality for PD.

In summary, oral therapy has no established role in modifying the course of PD. Currently, the AUA guideline does not recommend the use of any of the listed oral therapies.[38] Clinicians may offer oral nonsteroidal anti-inflammatory drugs for pain control during the active phase, but they should not offer vitamin E, tamoxifen, procarbazine, omega-3 fatty acids, or vitamin E combined with L-carnitine. Contemporary evidence has not demonstrated clinically meaningful improvements in curvature or plaque with oral agents, and patient counseling should reflect these limitations if a provider chooses to offer these agents as treatment.

Topical agents

Topical agents for management of PD date back to the earliest descriptions of the condition, with La Peyronie—as mentioned earlier—using holy water washings as a form of treatment.[5] Tinctures of iodine and mercury were touted as a complete success in the late 1800s. Potassium iodide, reported in France in 1840, is the earliest documented topical agent used for PD. In 1876, two patients exposed to hypothermia were treated with topical bromide of potash in camphor water and were directed to avoid cold weather; both reportedly achieved a complete recovery.[39]

Additional topical regimens emerged in subsequent decades. For example, an 1878 case series reported treatment using topical mercury alone, iodine tincture, and a combination of mercury and iodine, alongside small doses of oral medication. The topical mercury alone was said to have cured the induration within 3 weeks.[40] Later, in 1907, fibrinolysin-based therapy was first documented in Germany, marking another development in topical treatments.[17] However, few advances occurred in topical therapy until a 1960 study, when histamine iontophoresis was introduced.[17] This study claimed that the plaque could be completely resolved in as few as two to three sessions. In 1967, a similar iontophoresis technique was trialed using steroid cream. In this study involving 12 patients, softening of the plaque was observed in all but one case; however, none experienced complete resolution.[41] Later, in 1983, beta-aminopropionitrile was tested but did not prove to be a promising treatment modality.[17]

Studies regarding topical drug delivery resurfaced in the early 2000s. In 2002, concerns about verapamil gel's ability to penetrate the TA were specifically investigated. In this study, patients scheduled for PP implantation were instructed to apply topical verapamil the night before and morning of surgery. Tunical samples were obtained intraoperatively, and no verapamil was detected in the tissue, leading researchers to conclude that topical verapamil alone lacks a scientific basis for treatment of PD.[42] To address this concern, a 2004 study combined verapamil with dexamethasone using transdermal electromotive drug administration (EMDA) in 73 patients, demonstrating greater improvement in penile curvature in the treated group compared with the placebo group (lidocaine and dexamethasone).[18,43] However, a 2007 study revealed contradictory findings, showing that EMDA with verapamil resulted in no improvement in penile curvature.[18] A double-blind pilot study published in 2007 evaluated 15% topical verapamil gel for 3 months in 18 patients per group (compared to placebo), demonstrating a greater improvement in curvature with the active agent. However, there was significant heterogeneity in disease duration and degree of curvature in the subjects.[18,44]

In 2016, a randomized, prospective pilot study evaluated a new topical treatment called H-100 (containing nifedipine and superoxide dismutase) in 22 patients with acute-phase PD. The study reported some reduction in penile curvature in the treatment group compared with placebo.[18,45] More recently, a single RCT involving 186 patients with PD, published in 2019, evaluated treatment with coenzyme Q_{10}. This study reported subjective improvement in curvature, plaque size, and International Index of Erectile Function scores but observed no improvement in pain.[19,46]

In summary, none of the major organization's guidelines, including the AUA, the ISSM, and the EAU, currently recommend topical therapy as treatment for PD.[18] However, in the early stages of PD (before plaque hardening and calcification), some of the topical agents may decrease curvature and pain.[18,19]

External treatment for PD

As reported by Mohede et al.,[17] the first stand-alone external treatment for PD was electricity, as described by Van Buren in an 1874 textbook. Subsequent developments included investigations into ionization (attributed to Lavenant by Zislin in 1911), X-radiation (Bernasconi in 1912), and ultraviolet light (LeFur in 1912). Radium treatment was reported by Kumer in 1922, followed by diathermy by Wesson in 1943. In 1967, Heslop published the use of ultrasound for PD, and, in 1985, Puente de la Vega reported on the application of laser therapy. In 1989, Bellorofonte et al. described the use of lithotripsy to treat severe cavernous fibrosis due to PD.[17] In 1971, Frank and Scott reviewed ultrasound treatment for PD plaques in studies published up to that point and presented their own experience with 25 patients, primarily based on subjective patient reports.[47] Extracorporeal shock wave therapy (ESWT) has been demonstrated to cause plaque damage and, via mechanotransduction, to increase nitric oxide and vascular endothelial growth factor levels,[47] potentially leading to plaque resorption.[18] Three RCTs using

this treatment for PD were published between 2009 and 2013, involving a total of 238 patients. While two of these studies reported improvement in pain, none revealed changes in penile deviation or plaque size.[18]

Currently, the AUA guideline does not recommend external treatment modalities, as they have not been proven in RCTs. Specifically, clinicians should not use ESWT or radiotherapy to reduce curvature or plaque.[38]

ILI therapies

Background and history of ILI therapies

Intralesional injection (ILI) therapies include any treatment that is directly injected into the penis via a needle or other similar means. Although some have broadened the definition to include other mechanical/electrical means of facilitating penetration of therapies through the skin (eg, iontophoresis), the current historical summary is restricted to the narrower description. Justification for ILI is based on several concepts, including a relative ease of directly accessing the diseased portion of the penis (PD plaque) as well as the ability to deliver higher concentrations of an active agent than what may be otherwise achievable via topical or oral approaches.

Although the use of ILI therapies may date to well before the 1900s, the first known published report was in 1901, when ILI mercury and iodides were administered.[48] Interestingly, up until this point, mercury had been repeatedly utilized as an oral or topical treatment, beginning with the original descriptions by La Peyronie (1743) and again in the late 1800s by Curling and colleagues.[49] Later treatments included the enzyme trypsin (1922), followed by cortisone and hyaluronidase (both 1954), parathyroid hormone (1975), orgotein (1981), CCH (first used in 1985 and approved by the Food and Drug Administration [FDA] in 2013), prostacyclin (1988), interferon (IFN) alpha-2b (1991), verapamil (1994), nicardipine (2010), and hyaluronic acid (HA, 2015).[50-61] See Table 2 for a list of notable historical events related to ILI therapies. Although each of these treatments had mechanisms that were hypothesized to target one or more underlying mechanisms of penile fibrosis, only corticosteroids, IFN, verapamil, CCH, and HA were more broadly adopted and are herein described in further detail.

Corticosteroids have long been recognized to reduce fibrosis and scar formation via various mechanisms, including anti-inflammatory pathways.[62] Since their discovery, steroids have been used in numerous ways, such as topical dermatologic therapies, oral medications for fibrosing conditions like retroperitoneal fibrosis, and injectable agents.[63,64] In 1954, Teasley and colleagues first reported their use for PD treatment.[51] The therapy was subsequently popularized over the next 20-30 years, with several additional publications describing varying results. However, data from an RCT in 1998 demonstrated no improvements over saline (placebo) alone and suggested that the mechanical administration of the therapy may account for the majority of improvements observed.[65]

Given the limited improvements and the availability of alternative agents with more favorable long-term side-effect profiles, the use of ILI corticosteroids fell out of favor by the mid to late 1990s. Around this time, the use of ILI IFN was first reported by Nseyo and colleagues.[58] Although the underlying mechanisms for improvements were never adequately described, hypothesized benefits included immunogenic reactivation potentially stimulating the production of endogenous collagenase or activating the body's natural immune reaction to the disease site. Similar to ILI corticosteroids, ILI IFN was supported by multiple published retrospective series, nearly all of which demonstrated improvements compared to baseline. Arguably, the most important clinical study of this drug was released in 2006, involving 103 men treated in a prospective, multicenter, placebo-controlled (saline), parallel-arm fashion.[66] Results demonstrated statistically superior curvature and pain improvements with IFN compared to ILI saline. However, despite these early data, the use of IFN remained limited, likely due to its distinct side-effect profile of short-term flu-like symptoms, higher cost, and lesser availability compared with another commonly used therapy, ILI verapamil.

The use of ILI verapamil was first described by Levine and colleagues in 1994.[59] In contrast to ILI IFN, verapamil was readily available, inexpensive, and resulted in no appreciable adverse events. Although a clear mechanism for ILI verapamil was never fully demonstrated *in vitro*, it was hypothesized to treat PD by reducing collagen secretion from fibroblasts and by increasing endogenous collagenase activity. Despite several retrospective studies and a relative wide-spread adoption of the treatment, few high-level investigations were ever published. In the only randomized, placebo-controlled study, Shirazi and colleagues noted no differences in plaque size, pain, curvature, or other relevant outcomes when comparing ILI verapamil to saline.[67] A later study by Levine and colleagues reported outcomes of 77 men randomized to 10 mg of verapamil administered in three separate volumes (4 mL, 10 mL, 20 mL).[68] Results demonstrated statistically better results in the 20-mL arm, with no statistical benefits observed in the lower-volume groups compared to baseline. Together, these two reports suggest that any benefits from ILI verapamil treatment are likely due to the injection volume or mechanical trauma rather than the drug's pharmacologic effects. As such, findings with ILI verapamil mirror the conclusions previously reported by Cipollone and colleagues in their study of ILI corticosteroids.[65]

Arguably, one of the most notable events in the history of PD was the introduction of ILI CCH. Although Gelbard and colleagues first reported ILI CCH as a potential therapy for PD in 1980, including a subsequent pilot study in 1985, it was not widely adopted until after its FDA approval in 2013.[56,69] In contrast to other off-label treatments, CCH has been demonstrated to conclusively disrupt the collagen with PD plaque, resulting in diminished plaque sizes and improvements in PD curvature and morphology.[70] Following FDA approval, CCH was rapidly adopted (where available) and surpassed all other ILI therapies combined.[71] Although initial reports described relatively limited improvements (6° improvement over placebo), several notable advancements in technique, such as combining treatment with PTT, injecting at the point of maximal curvature, and adjusting the dosage, have led to better outcomes, including mean improvements of up to 58% in one series.[72,73]

The efficacy of ILI CCH has been reported in numerous case series since its release. Although multiple series have documented absolute changes in penile curvature with treatment, relatively few have addressed other key clinical metrics, including whether the treatment is considered meaningful by patients or whether subsequent surgery is required. In the earliest study reporting on the meaningfulness of CCH, 79% of men receiving treatment felt that the therapy was

Table 2. Notable historical events relating to intralesional and traction therapies for the treatment of Peyronie's disease.

Date	Event
Intralesional therapies	
1901	Mercury and iodides
1922	Trypsin
1954	Corticosteroids
1954	Hyaluronidase
1975	Parathyroid hormone
1981	Orgoteine
1985	Collagenase *Clostridium histolyticum*
1988	Prostacyclin
1991	Interferon alpha-2b
1994	Verapamil
2010	Nicardipine
2013	FDA approval of collagenase *C. histolyticum*
2015	Hyaluronic acid
Penile traction therapies	
2008	First study of first-generation PTT device
2010	FastSize PTT device removed from market by the FDA
2011	First description of PTT before penile prosthesis
2012	First description of PTT after penile plication
2012	First-generation PTT combined with verapamil
2014	First description of PTT as preventative therapy in active-phase PD
2015	First-generation PTT combined with interferon alpha-2b
2017	First-generation PTT combined with collagenase *C. histolyticum*
2017	Second-generation PTT released
2019	Second-generation PTT combined with collagenase *C. histolyticum*
2019	Second-generation PTT combined with collagenase *C. histolyticum* in ventral curvatures
2023	Second-generation PTT combined with novel collagenase *C. histolyticum* techniques

Abbreviations: PTT, penile traction therapy; FDA, Food and Drug Association; PD, Peyronie's disease.

meaningful overall.[74] Unsurprisingly, men who achieved greater curve improvements were more likely to report that the treatment was meaningful; in fact, over 90% of men achieving ≥30° improvements reported that the treatment was meaningful overall. These findings were supported by subsequent larger series, which similarly reported meaningfulness in the 74%-83% range, including among other cohorts such as men with ventral curvatures.[75]

The earliest report examining the subsequent need for surgery following CCH treatment was published in 2016.[76] Among the 31 men included in the report, 57% ultimately felt that CCH prevented the need for surgery, with 52% stating that the treatment was able to restore penetration. Since that time, multiple changes to technique have further improved outcomes of CCH treatment. An RCT was conducted to evaluate the overall satisfaction of men with PD who underwent surgery plus PTT (RestoreX, PathRight Medical, USA) versus CCH plus PTT (RestoreX). This study demonstrated non-statistically higher satisfaction rates in the injection cohort, with 50% of the men treated with CCH being very satisfied versus 21% in the surgery cohort ($P = .08$).[77] Interestingly, only 5% of men after CCH treatment indicated they would have preferred surgery if given the choice again, with no men in the CCH arm electing to subsequently undergo surgery to date (5-year follow-up). In the largest series published to date, of 509 men who completed at least one series of CCH, 69% felt that the treatment prevented surgery, 38% were unsure, and only 9% indicated that it did not prevent surgery.[73]

More recently, a potential resurgent role for ILI HA has also been reported.[61] Similar to IFN and verapamil, the specific mechanism of action for this therapy has not been elucidated. However, given its application as a potential *filler* in other body locations, some of its benefits may relate to a mechanical expansion of diseased tissue through fluid absorption. This may then counteract the contraction effect of the PD plaque and result in (at least) a perceived correction of the curvature. HA is also commonly used as a *filler* in hourglass/indentation-type deformities to achieve esthetic improvements. However, HA is known to provide only temporary benefits, and it remains unclear whether ILI HA can achieve durable outcomes similar to those of CCH.[78] Several comparative meta-analyses have highlighted the benefits of ILI HA, demonstrating short-term results superior to verapamil but similar to or worse than those of IFN and CCH.[79,80]

Challenges with ILI therapies

Although the concept of ILI therapies is well established, several historical and notable issues have hindered its widespread adoption. ILI treatments require direct injections into the penis, which often deter many men from seeking treatment. Similarly, given the off-label nature of most injection therapies, financial coverage of the various therapies is often limited. Some therapies are also unavailable in all regions worldwide, with CCH notably being largely restricted to the United States at the time of publication. PD also remains a poorly understood condition, with limited knowledge of inciting molecular events and treatments potentially disrupting active disease processes. This gap in knowledge—namely, the lack of a clear understanding of the disease pathogenesis—hinders the selection of appropriate ILI agents and the development of effective treatments. Similarly, since many men present several months after onset of the condition, ILI treatments that are effective in the early disease state may be less effective later (and vice versa). ILI therapies also remain highly specialized, with relatively few specialists

available with extensive treatment experience. This has led to a limited number of high-level publications and studies with predominantly small sample sizes.

In summary, ILI therapy can be offered as a primary treatment modality in appropriately selected patients. CCH is the only FDA-approved intralesional agent to treat penile curvature but not pain or ED. Other off-label options, including IFN and verapamil, may be used with specific counseling regarding potential side effects, efficacy, and cost limitations.

Penile traction therapies

Background and history of PTT

PTTs have likely been used for thousands of years, with anthropologic descriptions identified among multiple cultures throughout the world. Extracts from the Kama Sutra described an ideal sexual partner as one having larger genitals and recommended tying weights to the shaft of the penis to increase length (along with insect bites to cause direct inflammation).[81] Similarly, Peruvian tribes were known to use weights to stretch the penis, while Romans and Greeks in Europe employed forms of traction therapy to stretch the foreskin.[81] The historical practice of *jelking* (unclear origins) similarly involved the performance of manual traction during a partial erection to achieve penile lengthening.[81]

Despite the widespread and long-standing use of these above-mentioned therapies, the specific mechanisms by which lengthening is achieved are poorly understood, with no basic science investigations performed to date. In contrast, several animal studies have demonstrated mechanisms through which PTT improves penile deformity and EF, such as increasing matrix metalloproteinase 8, decreasing smooth muscle alpha-actin, increasing endothelial nitric oxide synthase, and possibly affecting other antiapoptotic and antifibrotic pathways.[82-84]

From a categorical standpoint, due to significant differences in design and study outcomes, PTT devices are generally classified as first- or second-generation devices, with all first-generation devices employing similar spring-like mechanisms and limited ability to dynamically lengthen or counterbend while attached. First-generation devices include Andropenis (Andrometical, Spain), Penimaster (MSP Concept GmbH & Co. KG, Germany), X4 Labs (X4 Labs, Canada), Phallosan Forte (Swiss Sana AG, Switzerland), and other devices that employ similar traction mechanisms. These first-generation devices require 2-9 h of daily use for 3-6 months to achieve benefits.[85-89] In contrast, second-generation devices (RestoreX, RestoreXL, PathRight Medical, USA), which require 30 min of daily use, apply greater traction forces, provide dynamic lengthening, and utilize counterbending to correct curvature and deformity.[90]

Data from PTTs

The first pilot study evaluating the efficacy of PTT in PD men was published in 2008 ($n = 10$) and reported no statistically significant improvements in length and curvature.[85] Interestingly, the device was subsequently seized by the FDA in 2010 due to the company's failure to adhere to appropriate labeling and manufacturing regulations. Subsequent studies of two other first-generation PTT devices showed variable benefits, with 2 of the 3 publications demonstrating no statistically significant curvature improvements in men with stable-phase PD and the third publication exhibiting several notable methodological and statistical reporting issues.[87-89] The first second-generation PTT device was released in 2017, with a subsequent RCT demonstrating statistically significant improvements in length, curvature, and indentation/hourglass deformities.[90] Since then, several additional studies have confirmed these findings, including across different populations.[91-93]

In 2012, PTT was also evaluated as a possible combination treatment, with three studies reporting outcomes of first-generation devices used in combination with verapamil, IFN, and CCH, all of which failed to demonstrate statistically significant improvements in curvature.[94-96] Several studies have subsequently reported outcomes of second-generation devices combined with CCH, demonstrating statistically greater results compared to ILI therapy alone or in combination with first-generation devices.[73,77,97-99] In the largest study evaluating comparative outcomes of various traction therapies combined with CCH, Alom and colleagues reported on 275 men who underwent at least one series of CCH.[97] Men were categorized into three groups: CCH alone, CCH plus first-generation devices (including Penimaster, X4 Labs, Andropenis, and others), and CCH plus RestoreX. The results demonstrated no significant differences between CCH alone and CCH combined with first-generation devices in regard to penile length and curvature improvements. However, the combination of CCH with RestoreX was associated with an 11.8-fold, 4.4-fold, and 7.5-fold greater likelihood of achieving $\geq 20°$ curvature improvements, $\geq 50\%$ curvature improvements, and $\geq 20\%$ length improvements, respectively.

In addition to the above-mentioned uses, two small retrospective studies published in 2011 and 2012 reported modest outcomes of PTT, both as a preoperative therapy before PP placement and as a postoperative therapy following PD surgery.[100,101] A summary of notable events related to traction therapy is shown in Table 2.

In summary, PTT has shown promising results, especially when used in combination with intralesional therapy. The AUA, ISSM, and ESSM do not specifically endorse the use of this therapy, although they recognize the promising results so far.

Surgical approaches for PD: Historical and current

Grafting techniques

The surgical correction of PD using grafts has evolved substantially since the mid-20th century (Figure 3). In 1943, Lowsley described the first known use of grafts in PD, applying autologous fat pads after excision of fibrous septal tissue.[102] While innovative, these fat grafts lacked structural integrity and tensile strength. By 1973, de-epidermized dermofat grafts from the thigh were used to better replicate tunical properties, and full-thickness grafts with the exclusion of fat were introduced as an alternative approach.[103,104]

In 1976, saphenous vein grafting was described, with the idea of utilizing the vein's elastic properties and biocompatibility. Further modification included the use of a lozenge-shaped graft and the first transverse plaque excision, shifting from the previously used longitudinal approach.[105] By 1977, Kelami recommended using preserved human dura mater for grafting, and, in 1980, he presented an age-based treatment strategy: grafting for younger patients and prosthesis-only solutions for older patients with compromised EF.[106,107]

A major conceptual shift occurred in 1989 when Sampaio and Passarinho introduced plaque incision and graft. I-shaped incisions were performed to relax fibrotic plaques,

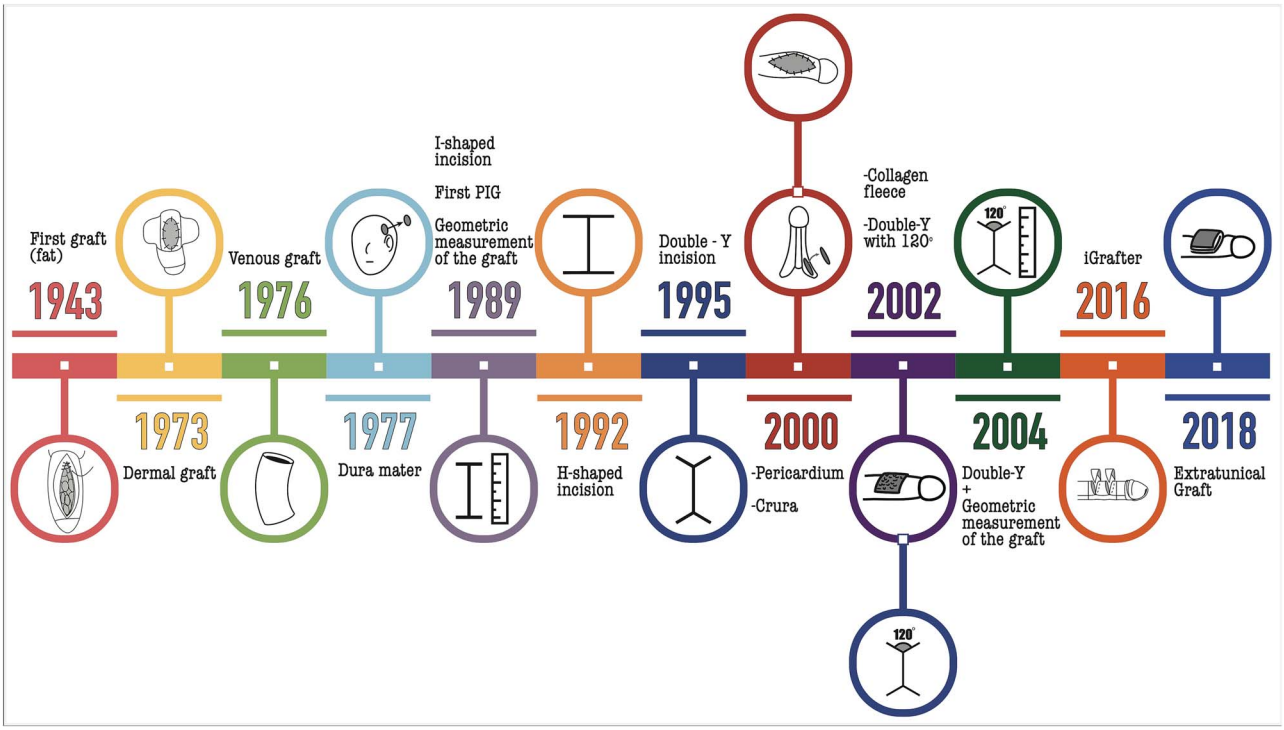

Figure 3. Timeline of landmark developments in grafting surgery for Peyronie's disease. Abbreviation: PIG, plaque incision and grafting.

using geometric calculations to determine graft size based on differences between the long and short penile sides.[108] This established the principle of minimizing the graft area to reduce veno-occlusive dysfunction and thereby preserve EF. By 1992, refinements to the technique were established by advocating a single central graft placed after an H-shaped incision precisely at the point of maximum curvature.[109] These methods became a cornerstone in modern PD surgery. Further innovation followed with the proposed double-Y relaxing incision in 1995, aimed at reducing the risk of corporal narrowing by adding to the middle incision to preserve the width of the corpora cavernosa.[110] In 1998, the H-incision technique was combined with autologous saphenous vein grafts, assembling large venous patches using clips and refining suturing protocols.[111]

Another major leap forward occurred in 2000 when Hellstrom introduced Tutoplast human pericardium grafts, which offered low immunogenicity and consistent outcomes.[112] This product's use remains ubiquitous to this day. That same year, grafts from the crural segment of the corpora cavernosa were proposed, a method histologically similar but limited by tissue availability.[113] The introduction of collagen fleece (TachoComb) in 2002 enabled sutureless application via manual compression, reducing operative time.[114] Subsequent modification of the double-Y incision technique involved using bifurcated transverse incisions and longitudinal traction to determine graft size by direct observation.[115,116] In 2004, continued innovation of grafting strategies for lateral curvatures incorporated trapezoidal grafts and integrated geometric sizing principles to dorsal and ventral curvatures.[117] These innovations in grafting techniques and materials paved the way for modern collagen-based applications later in the decade.

In 2011, early clinical use of TachoSil, an equine collagen version of the same material, yielded promising outcomes.[118] Three-dimensional (3D) penile modeling in 2014 demonstrated that H- and double-Y incisions can distort penile geometry, leading to recommendations to trim the triangular excess to allow proper graft fitting.[119] Shortly after in 2016, the iGrafter software was developed by Miranda et al., facilitating real-time planning for incision and graft sizing.[120] This technique corrected both uniplanar and multiplanar deformities with or without hourglass using lozenge-shaped grafts that required only half the area of double-Y grafts, theoretically reducing postoperative ED.[121] Finally, in 2018, Lue et al. introduced extratunical grafting (ETG), applying grafts externally to the TA to correct hourglass deformities while minimizing neurovascular and tunical injury. ETG allowed for deformity correction without violating the TA of the corpora.[122]

In summary, plaque incision or excision with grafting is indicated in patients with stable disease, preserved EF, and complex deformities not amenable to simple plication, such as severe curvature (typically >60°), hourglass, or hinge deformities. The procedure aims to preserve penile length. The recommendation for grafting in these settings is supported by the EAU, which explicitly cites curvatures exceeding 60°, and is similarly endorsed by the AUA and the ESSM.[38,123,124]

PP implantation

PP surgery transformed the management of PD, particularly in cases with significant deformity and ED (Figure 4). In 1967, dorsal silicone rods were introduced and placed between the Buck's fascia and corpora cavernosa, and, by 1972, this approach advanced to intracavernosal single-rod placement postplaque excision, which notably improved integration and comfort.[125,126] In 1977, the first combined prosthesis insertion with plaque incision without grafting was performed.[127] That same year, successful correction of penile curvature solely

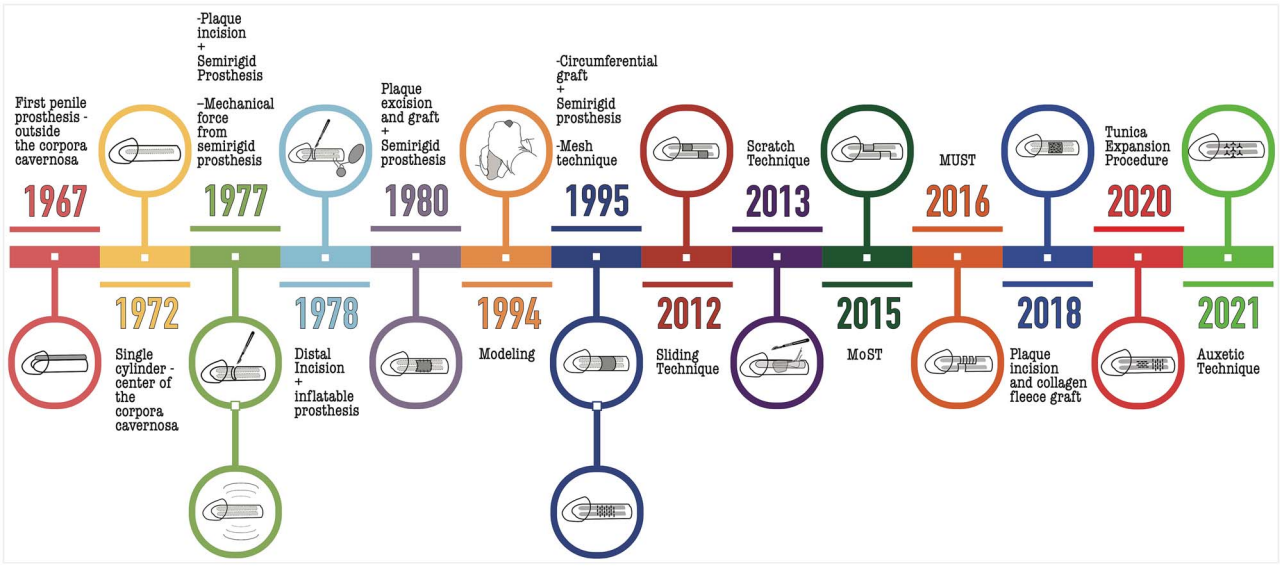

Figure 4. Timeline of landmark developments in penile prosthesis surgery for Peyronie's disease. Abbreviations: MUST, multiple-slit technique; MoST, modified sliding technique.

by PP implantation was documented.[128] In 1978, Furlow introduced inflatable PP implantation combined with a distal transverse incision to address curvature more effectively,[129] an approach that predated the later report in 1981.[130] By 1980, it was observed that the mechanical force exerted by the prosthesis typically resulted in gradual straightening over 2-3 months, and thus conservative management for residual curvatures was advocated.[107] That year also marked the first description of combining plaque excision, dermal grafting, and malleable PP implantation in a single operation.[131]

A major advancement occurred in 1994, when Wilson et al.[132] enhanced curvature correction through intraoperative modeling—manually bending the penis postprosthesis insertion to achieve alignment. This innovation built upon the mechanical force principles previously outlined and remains foundational in contemporary prosthesis-based correction strategies. In 1995, two alternative methods were introduced. One employed circumferential incisions of the corpora with graft closure, enabling shaft telescoping to correct shortening and deformity.[133] The other introduced the mesh-incision technique, using multiple transverse incisions to relieve tunical tension without the need for excision or grafting.[110]

Further refinements emerged in 2012 with the sliding technique, which combined longitudinal and semicircular incisions with split grafts to elongate the shaft while preserving neurovascular integrity.[134] Before the sliding technique was further refined, another innovation emerged in 2013: the scratch technique, which mechanically disrupts plaques intraoperatively by using blunt or sharp tools on the internal aspects of the TA. This approach enhanced tunical flexibility and reduced residual curvature while avoiding grafts and minimizing urethral injury during subsequent modeling.[135] In 2015, the modified sliding technique eliminated the need for grafts by using Buck's fascia for tunical closure.[136]

In 2016, the multiple-slit technique was developed, which involved distributing transverse corporal incisions aimed at improving symmetry and reducing bulging.[137] In 2018, Hatzichristodoulou performed the first technique combining inflatable PP implantation with grafting, using TachoSil to seal the tunical incisions.[138] Two years later, in 2020, Egydio introduced the tunica expansion procedure (TEP),[139] a graft-free method building on the mesh-incision concept but incorporating longitudinal incisions for hourglass deformities and transverse incisions for curvature correction. Unlike the original mesh technique, which used only transverse incisions focusing solely on curvature correction, TEP strategically combined both incision types to achieve total anatomical restoration.

In 2021, the auxetic technique was developed by Miranda, applying principles from materials science through star-shaped incisions that expand bidirectionally under tension (Figure 5). Bench models and 3D simulations confirmed its biomechanical superiority over traditional mesh incisions.[140] This technique enabled simultaneous length and girth gains, overcoming the limitations of the mesh technique, with data confirming its efficacy in 2024.[141] This method corrected uniplanar, multiplanar, and hourglass deformities, achieving significant volumetric enhancement without grafts. Outcomes showed high rates of patient satisfaction, low rates of complications, and strong reproducibility across diverse anatomical abnormalities. However, further studies are still needed to solidify its long-term value.

In summary, PP implantation is recommended in patients with PD when ED is severe and unresponsive to conservative measures, including oral pharmacotherapy, intracavernosal injections, or vacuum devices, or when penile deformity itself prevents satisfactory intercourse. Inflatable PPs are preferred due to their superior functional outcomes, and adjunctive intraoperative techniques (eg, modeling) may be employed if residual curvature persists. These indications are consistently endorsed by the AUA, the EAU, and the ESSM.[38,123,124]

Plication procedures

The first report of a surgery to correct PD was published by M'Clelland in 1827 (Figure 6). The procedure involved a large excision of an ossified plaque closed with a longitudinal suture of the TA.[142] In 1836, Lucien Baudens reported the first documented case of surgical plication for penile

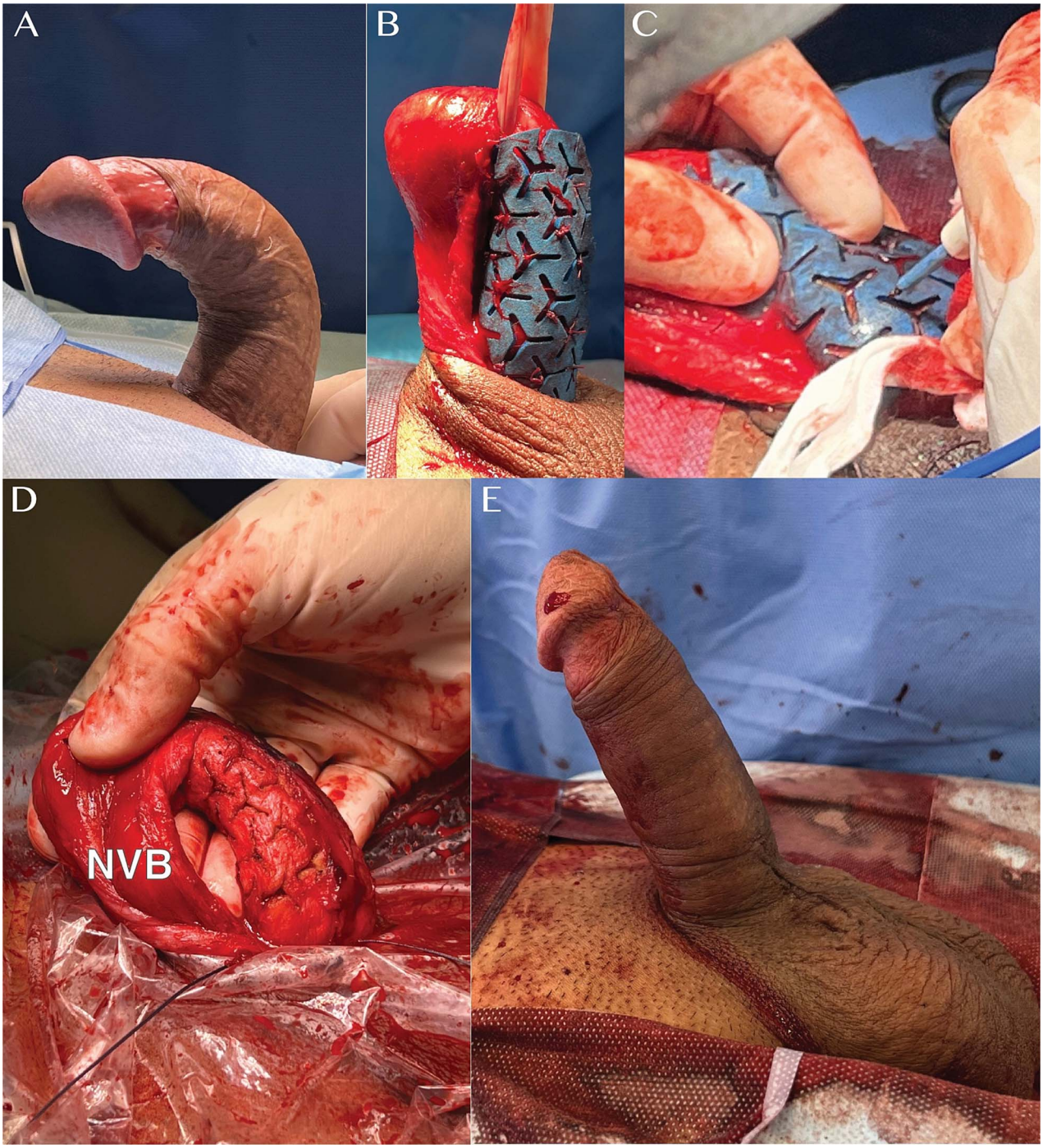

Figure 5. Application of the auxetic technique to correct penile curvature. (A) Artificial erection induced revealing 100° dorsal curvature. (B) Auxetic stencil fixed over the corpora cavernosa. (C) Tunica albuginea incision guided by the auxetic stencil, using the electrical scalpel in pure cut mode – 10 W. (D) Final result after removing the auxetic stencil (NVB). (E) Final result after inflatable penile prosthesis implantation. Abbreviation: NVB, neurovascular bundle. *Reproduced with permission from JSM. 2024; 21 (Suppl 6).*

curvature. His patient, a Napoleonic war soldier, developed penile curvature following a gunshot wound to the genitals. The curvature was corrected by incising the TA on the concavity's contralateral side and inserting a linen thread to induce fibrosis, thereby straightening the penis.[143] This technique preceded the use of a shortening technique to correct an acquired penile curvature by 143 years.[144,145] Both authors reported adequate outcomes, with their patients being able to resume intercourse after their surgeries.[142,143]

In 1901, Sachs theorized that shortening the longer (convex) side of the penis was the most effective method to correct penile curvature.[146] Interestingly, these pioneers explored the concepts of lengthening and shortening procedures to correct penile curvature more than a century before the establishment of modern guidelines.[38,142,143,147]

It was not until the late 1970s that surgical procedures focused on excising the plaque and lengthening the shorter (concave) side, with or without grafting.[102,148-151] However,

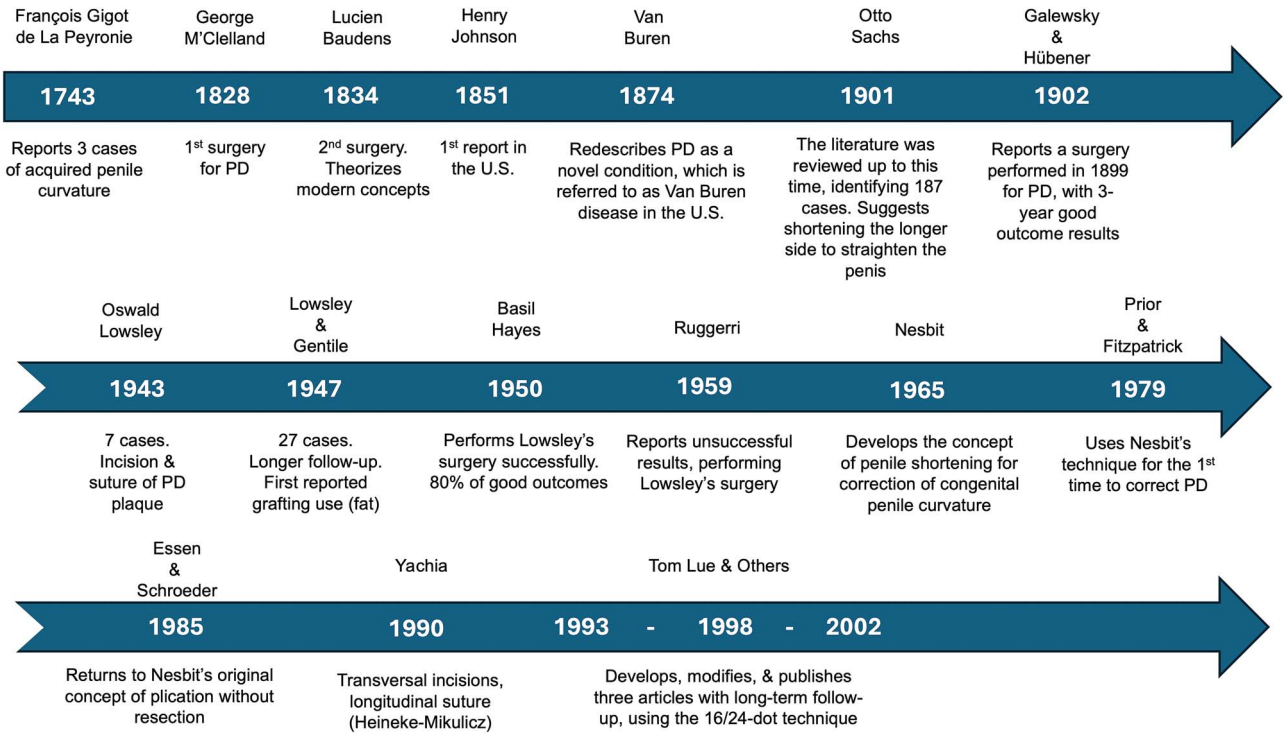

Figure 6. Timeline of landmark developments in penile plication procedures for PD. Abbreviation: PD, Peyronie's disease.

in 1979, an alternative approach was proposed: shortening the longer convex side of the corporal body.[144] Using a technique initially developed by Nesbit in 1965 for correcting congenital chordee without hypospadias,[152] the authors reported the first sizable modern series of shortening procedures to correct PD.[144] Small ellipses were excised on the convex side and sutured with nonabsorbable sutures, thereby shortening and straightening the penis. All patients achieved complete penile straightening, with 87% preserving their EF. Despite these positive results, this approach faced criticism, with the publication's editor commenting that patients may become unhappy with a shorter penis.[144]

In the 1980s, Nesbit's original concept was revisited and further developed. Despite the criticisms,[144,153] the application of Nesbit's surgery for PD correction became more popular, with multiple authors creating variations of Nesbit's method.[145,154-158] From the many proposed modifications, three are noteworthy for their innovation and influence.[145,156,158] In 1985, a series of patients were treated by imbricating and suturing the TA with nonabsorbable sutures on the convex side of the penile curvature without TA resection.[145] The authors reported excellent outcomes in all patients. Interestingly, Nesbit had initially used the plication-only method but later shifted to tissue excising and suturing after he observed an early recurrence. Five years later, another modification was proposed based on the Heineke–Mikulicz principle: longitudinal TA incisions closed transversely. This technique avoided excision and neurovascular mobilization, reducing the risk of complications. Despite promising results, the lack of long-term follow-up was a limitation of this report.[156] In 1992, the 16/14-dot plication technique was described by Lue et al., with further modifications reported over the ensuing years.[157,158] A major update came in 2002, when they presented outcomes from a case series of 132 patients treated using the 16/24-dot plication method. While overall satisfaction rates were 91%, a notable 41% of patients identified penile shortening as their primary complaint.[159]

Conclusion

PD is a localized FP condition of the penis and has been recognized for millennia. A myriad of oral and topical treatments have been advocated over time, usually anecdotally with short duration, small populations, and variable outcome methodologies being reported. Understandably, major academic societies (AUA, SMSNA, ISSM, EAU, and ESSM) no longer recommend these options in their guidelines. Intralesional and traction therapies have documented benefit in afflicted individuals. Surgery still has an important role in severe structural abnormalities with prosthetic use when ED is documented. Future PD research needs to incorporate recent advances and strategies that have been developed in the other common FP conditions. Further study of fibrosis pathways will ultimately lead to prevention and novel treatments for men who suffer with PD.

Disclosures

- Landon Trost is the inventor of the RestoreX penile traction device; Mayo Clinic holds the rights to the related patent and technology. He is a shareholder in PathRight Medical, held in a blind trust. He has received research grants from Endo Pharmaceuticals (all investigator-initiated grants).
- Alexandre Miranda developed the iGrafter software and is the owner of Alexandre Miranda Serviços Médicos LTDA, a medical services company based in Brazil.
- Ronald Lewis serves as Chair of the ISSM History Committee and is a Past President of ISSM.
- Wayne J.G. Hellstrom is a consultant for Endo Pharmaceuticals, serves as a Committee Member for ISSM, and is a Past President for ISSM.

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Author contributions

Conception and design: W.J.G.H. and R.L. Acquisition of data: W.F., D.M., R.L., L.T., B.M., A.M., and W.J.G.H. Analysis and interpretation of data: W.F., D.M., R.L., L.T., B.M., A.M., and W.J.G.H. Drafting the manuscript: W.F., D.M., F.L., L.T., B.M., A.M., and W.J.G.H. Revising the manuscript: W.F. and W.J.G.H. Final approval of the completed manuscript: W.F., D.M., R.L., L.T., B.M., A.M., and W.J.G.H.

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