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Medical treatments of Peyronie's disease: past, present and future.

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Introduction

Peyronie's disease (PD) is a benign fibroproliferative disorder, which causes the formation of plaque in the tunica albuginea of the corpora cavernosa in the penis. The disease is named after François Gigot de la Peyronie (1678-1747), although Fallopius and Vesalius had already described the disorder in 1561 (1).

Since the time of Peyronie, who sent his patients to the holy water of Baragès in the French Pyrenees (2), many nonsurgical empirical approaches have been tried in an attempt to cure PD, but there is still no effective cure. This is mainly due to a lack of understanding concerning the biology and pathology of PD (3). Once a calcified or even ossified plaque has developed, there is no nonsurgical treatment to make it disappear.

In 2004, Ralph and Minhas found 38 nonsurgical treatments of PD (4). At the time of writing, none of them has received a grade A recommendation under the American and European guidelines (5, 6). Collagenase from *Clostridium histolyticum* is the only drug approved by the US Food and Drug Administration and the European Medicines Agency for intralesional injection in patients with palpable plaque and dorsal or dorsolateral curvature greater than 30°, smaller than 90° and intact erectile function.

In the acute phase, PD is treated conservatively (non-steroidal anti-inflammatory medications may offer analgesia) and, in general, surgical approaches are only attempted after around one year in patients for whom the disease has not worsened for at least three months and who have a curvature that impedes sexual intercourse. During that waiting time, patients are often willing to undergo treatments. The effectiveness of these treatments, however, has not been proven in a three-arm study design (test treatment vs placebo vs no treatment) with an 18-month duration. In this article, we reflect on the past, present and future of nonsurgical treatments of PD, with the emphasis being on oral treatments.

Material and methods

An extensive literature search (*The Cochrane Library, PubMed/MEDLINE, Web of Science, EMBASE* and old German, Dutch, French and English medical books on male sexual functioning) was performed with the searches spanning until January 2018. The search included all medical interventions in patients with PD (or 'cavernosits', 'penile fibrosis', 'fibrous sclerosis of the penis', 'induratio penis plastica' or 'Van Buren's disease'), as reported in articles in any of the previously mentioned databases, or others found as references in articles and antiquarian books. We discuss our overall findings.

Results

In all consulted databases and references, researchers found a total of 48 nonsurgical interventions in articles published from 1743 to 2017. These included eleven external, eleven intralesional, seven topical and 23 oral interventions (Table 1). A further four of the treatments comprised a combination of two of the nonsurgical interventions.

Table 1. Historical overview of first reports about nonsurgical interventions for PD

(E = external; I = intralesional; O = Oral; T = topical)

Year	Therapy	O/T/I/E	Authors
1743	*Mercury and mineral water*	O	De la Peyronie (2)
1840	*Potassium iodide*	O/T	Ricord (7)*
1864	*Electricity*	E	Van Buren (8)*
1876	*Bromides and hyperthermia*	O/E	Hodgen (9)*
1878	*Mercury and iodides*	O/T	Curling (10)
1890	*Sulfur*	O	Dubuc (11)*
1896	*Copper sulfate*	O	O'Zoux (12)*
1901	*Salicylate and thiosinamin*	O	Sachs (13)*
1901	*Mercury and iodides*	I	Walsham (14)
1902	*Arsenic*	O	Reliquet (15)*
1907	*Fibrinolysin*	O/T	Waelsch (16)*
1910	*Ionization*	E	Lavenant: quoted by Zislin (17)*
1911	*Milk*	O	Van der Pool (18)*

1911	*X-radiation*	E	Bernasconi (19)*
1912	*Ultraviolet light*	E	LeFur (20)*
1922	*Trypsin*	I	Sonntag (21)*
1922	*Radium*	E	Kumer (22)*
1943	*Diathermy*	E	Wesson (23)
1943	*Di-sodium phosphate*	O	Wesson (23)
1949	*Vitamin E*	O	Scardino (24)
1954	*Cortisone*	I	Teasly (25)
1954	*Hyaluronidase and steroid*	I	Bodner (26)
1955	*Oestrogens*	O	Minder (27)
1959	*Potassium para-aminobenzoate*	O	Zarafonetis (28)
1960	*Histamine iontophoresis*	T	Whalen (29)
1963	*Prednisolone*	O	Chesney (30)
1967	*Ultrasound*	E	Heslop (31)
1967	*Dimethyl sulfoxide*	O	Persky (32)
1967	*Steroid iontophoresis*	T	Rothfeld (33)
1970	*Procarbazine*	O	Aboulker (34)
1975	*Parathyroid hormone*	I	Morales (35)
1981	*Orgoteine*	I	Bartsch (36)
1983	*Beta-aminopropionitrile*	T	Gelbard (37)
1985	*Collagenase*	I	Gelbard (38)
1985	*Laser*	E	Puente de la Vega (39)
1988	*Prostacyclin*	I	Strachan (40)
1989	*Lithotrypsy*	E	Bellorofonte (41)
1991	*Interferon*	I	Benson (42)
1992	*Tamoxifen*	O	Ralph (43)
1994	*Verapamil*	I	Levine (44)
1994	*Colchicine*	O	Akkus (45)
2001	*Carnitine*	O	Biagiotti (46)
2001	*Traction devices*	E	Scroppo (47)
2003	*PDE5-I & arginine*	O	Valente(48)
2006	*Pentoxifylline*	O	Brant (49)
2009	*Omega-3 fatty acids*	O	Safarinejad (50)
2010	*Nicardipine*	I	Soh (51)
2016	*Superoxide-dismutase nicardipine and emu oil*	T	Twidwell (52)

*Cited in (53)

Discussion

Nowadays, surgery is of minimal value in patients with peptic duodenal ulcers, pulmonary tuberculosis or anus carcinoma. For those disorders, effective nonsurgical treatments have replaced mutilating surgery. This is not yet the case for PD.

Throughout the past three centuries, many medical treatments have been tried, but nearly all were reported after clinical studies with a low number of patients and/or based on anecdotal experiences. In 1968, for example, Aron noted a regression of Dupuytren's disease in a patient who was treated with the cytotoxic procarbazine for Hodgkin's disease, and he suggested the use of this drug in fibroproliferative disorders (54). In the 1970s, investigators from France reported excellent results in patients with PD, but in Belgium, procarbazine had disappointing results (55, 56). It is interesting to note that many titles of the articles on PD treatments used the words 'new therapy'.

The modern era of trial and error in the medical therapy of PD began in 1949 with Scardino's report on the use of tocopherols (24). Teasly first reported successful intralesional corticosteroid injections in 1954 (25). However, because a widely accepted and effective medical treatment for PD was unavailable, research was primarily done by surgically-orientated urologists. They understandably focused on operation techniques, which led to them neglecting the pursuit of medical therapies. The only exceptions were the collagenase protocols of 1993 and the collagenase clostridium histolyticum (CCH) injection therapy in the last decade. Collagenase was the only subject of study in which the effects were evaluated in a randomized, placebo-controlled, double-blind manner. Moreover, this was preceded by animal studies (57). One of the few other animal studies showed a reduction of fibrosis in the tunica albuginea when the rats consumed pentoxifylline, L-arginine or any of three PDE-5 inhibitors (sildenafil, vardenafil, tadalafil) through drinking water (48). The authors hypothesized that the increase in NO and/or cGMP/cAMP levels by chronic administration of nitrergic agents or PDE inhibitors could be effective in reversing the fibrosis of PD and, more speculatively, other fibrotic conditions.

In the American and European guidelines, none of the options depicted in the table carries a grade A recommendation. Today, drugs such as carnitine, arginine and dimethyl sulfoxide (DMSO) belong to the domain of complementary and alternative medicine (CAM) in most European countries. Another alternative treatment available on the internet is bromelain,

which is the crude extract of pineapple and has fibrinolytic, antithrombotic and anti-inflammatory properties (58). However, there are no scientific data about its use by PD patients. According to the National Center for Complementary and Integrative Health in the US, bromelain is available as a powder, cream, tablet and capsule.

Overall, oral medical treatments are considered potentially effective in only the early phase of PD, that is, before plaque hardening and calcification occur. According to the current European guidelines, oral steroids, vitamin E and tamoxifen should be avoided completely as treatment. The American Urological Association (AUA) added procarbazine, omega-3 fatty acids and the combination of L-carnitine with vitamin E to their list of treatments to avoid. The remaining drugs for off-label use are pentoxifylline, a PDE-5-inhibitor and/or arginine, or a combination of these. The AUA guidelines from 2015 report that pentoxifylline (whether or not combined with intralesional verapamil and traction) can reduce pain and ED (6).

Since the release of the 2015 AUA guidelines, an Italian study showed that treatment that combined pentoxifylline with minor antioxidants (propolis, blueberries and vitamin E) and topical diclofenac was effective in patients with early-stage PD (59). This study also demonstrated that the clinical efficacy of pentoxyphyline was greater when administered both orally and locally through perilesional injection.

Current knowledge and new drugs for fibrosis

In all fibroproliferative diseases, the differentiation and activation of myofibroblasts is one of the most important processes. These cells are the main producers of collagen and other extracellular matrix components. They also contain α-actin, which is a protein that causes cell contraction and thus contributes to distortion and dysfunction (60). Myofibroblasts originate from locally-present fibroblasts or differentiated infiltrating fibrocytes (61). Fibrocytes are circulating connective tissue progenitor cells. The transformation of precursor

cells to myofibroblasts is influenced by various growth factors, cytokines and clotting factors. As the healing process progresses, the myofibroblasts will eventually disappear by apoptosis. It has been hypothesized that deregulation of this apoptotic process can occur, thus allowing more myofibroblasts to remain active (62). Addtionally, there are indications that epigenetic changes in fibroblasts or myofibroblasts may contribute to fibrotic changes (63, 64). Nowadays, as in PD, there are largely ineffective therapeutic options for patients with fibrotic diseases in general. New agents under investigation are pirfenidone, tyrosine kinase inhibitors, transforming growth factor-β, platelet-derived growth factor, interleukin-13 and lysyl oxidase-2 (65).

Pirfenidone is an expensive, small molecule that is available for oral use. The exact molecular mechanism of action is not completely explained. Based on in vitro studies, it is assumed that pirfenidone inhibits the proliferation and synthesis of pro-fibrotic and inflammatory mediators, and the collagen synthesis by fibroblasts and myofibroblasts. It is the first specific anti-fibrotic agent that is approved for the treatment of patients with idiopathic pulmonary fibrosis in Europe, Japan and the United States (66). New studies could show whether pirfenidone works in patients with fibrotic diseases other than idiopathic pulmonary fibrosis.

The protein tyrosine kinase inhibitor nintedanib seems to be successful in the treatment of patients with pulmonary fibrosis, while some forms of systemic sclerosis seem to decrease after treatment with the protein tyrosine kinase inhibitor imatinib mesylate (67, 68). These new treatment options, however, are not yet beyond phase II studies in patients with idiopathic pulmonary fibrosis. It remains to be seen whether these therapies can also be applied in the treatment of patients with other fibrosing disorders.

Concluding remarks

Many of the old and new drugs reviewed have a reasonable basis for their use, but the lack of basic research on the biology and pathology of PD makes it difficult to understand the working mechanisms. The most important goal of medical therapy is to prevent or halt the process of plaque formation and scarring. Patients typically present pain during the acute phase. If the plaque begins to harden, oral drugs will not be delivered. This is most likely due to the decreased vasculature. Therefore, pharmacotherapy should be initiated as soon as possible in the acute phase of PD.

Nowadays, patients may use pentoxifylline, a PDE-5-inhibitor, antioxidants or a combination of these off-label. Antioxidants belong to the domain of complementary and alternative medicine.

The search for new, well-tolerated and effective medical therapy has to continue. In the end, the management of PD should improve, with fewer patients needing surgery. In that respect, we strongly recommend close collaboration with nonsurgical experts in fibrotic diseases.

References

1. Hauck E, Weidner W, Nöske H. François Gigot de la Peyronie: the first complete clinical description of induration penis plastic. In: Schultheiss D, Musitelli S, Stief C, Jonas U, editors. Classical writings on erectile dysfunction An annotated collection of original texts from three millennia. Berlin: ABW Wissenschaftsverlag; 2005. p. 105–10.
2. De la Peyronie FG. Sur quelques obstacles qui s'opposent à l'éjaculation naturelle de la semence. Mém Acad Roy Chir. 1743;1:318–33.
3. Levine AL. Seeking answers on the quest for effective nonsurgical treatment of Peyronie's disease. Eur Urol. 2007;51:601-4.

4. Ralph D, Minhas S. The management of Peyronie's disease. Br J Urol Int. 2004;93:208-15.

5. Hatzimouratidis K, Eardley I, Giuliano F, Hatzichristou D, Moncada I, Salonia A, et al. EAU guidelines on penile curvature. Vol. 62, Eur Urol. 2012. p. 543–52.

6. Nehra A, Alerowitz R, Culkin DJ, Faraday MM, Hakim LS, Heidelbaugh JJ, et al. Peyronie's Disease: AUA Guideline. Vol. 3, J Urol. 2015. p. 745-53.

7. Ricord. Gaz. Des Hôpitaux. Bull Gen Ther Paris.1840;19:222-6.

8. Van Buren K. 1875. In: Textbook, dis G-U Org, Arch F Dermat Syph. 1875th ed. 1874, p. 572.

9. Hodgen. No Title. Trans Med Soc, Missouri. 1876;28:31.

10. Curling TB. Impotency. In: Diseases of the testis, spermatic cord and scrotum. 4th ed. London: J & A Churchill, 1878:460-5.

11. Dubuc. No Title. Ann Des Mal Des Orgn G-U. 1890;181.

12. O'Zoux. No Title. Ann Des Mal Des Orgn G-U. 1896;14:38-41.

13. Sachs. No Title. Wien Klin Woch. 1901;14:111-8.

14. Walsham WJ, Spencer WG. Sores on the penis. In: Spencer WG. Surgery: its theory and practice. 8th ed. London: J. & A. Churchill, 1903:1037.

15. Reliquet. No Title. Ann Des mal Des Orgn G-U. 1890;181.

16. Waelsch. No Title. Deut Woch, Münch Med Woch. 1906;55:1427-30.

17. Lavenant, Zislin (Quoted by). No Title. These, Paris. 1911.

18. Pool V der. No Title. Jour Of Cut G-U Dis. 1901;275 and 588.

19. Bernasconi. No Title. Rev Clin d'Urol, Paris,. 1912;1:53-6.

20. LeFur. No Title. 16th Sess l'Assoc Fr de l'Urol, Paris. October 1912.

21. Sonntag. No Title. Arch F Klin Chir. 1921;117:612-46.

22. Kumer. No Title. Dermat Woch. 1922;75:673-7.

23. Wesson M. Peyronie's disease, cause and treatment. J Urol. 1943;49:350-6.

24. Scardino P, Scott W. The use of tocopherols in the treatment of Peyronie's disease. N Y Acad Sci. 1949;52:390-6.

25. Teasly G. Peyronie's disease: a new approach. J Urol. 1954;71:611-4.

26. Bodner H, Howard A, Kaplan J. Peyronie's disease: cortisone- hyaluronidase-hydrocortisone therapy. J Urol. 1954;72:400-3.

27. Minder J. Über die Wirkung des Oestrogen-Hormontherapie bei der Induratio Penis Plastica. Oncologia. 1955;8:19.

28. Zarafonetis C, Horrax T. Treatment of Peyronie's disease with potassium para-amino benzoate (POTABA). J Urol. 1959;81:770-2.

29. Whalen W. A new concept in the treatment of Peyronie's disease. J Urol. 1960;83:851-2.

30. Chesney J. Plastic induration of the penis: Peyronie's disease. Br J Urol. 1963;35:61-6.

31. Heslop RW, Oakland DJ, Maddox BT. Ultrasonic therapy In Peyronie's Disease. Br J Urol. 1967;39:415-9.

32. Persky L, Stewart B. The use of dimethyl sulfoxide in the treatment of genitourinary disorders. Ann N Y Acad Sci. 1967;141:551-4.

33. Rothfeld S, Murray W. The treatment of Peyronie's disease with iontophoresis of C21 esterified glucocorticoids. J Urol. 1967;97:874-875.

34. Aboulker P, Benassayag E. Traitement de l'induration plastique des corps caverneux par la procarbazine (Natulan). J Urol. (French) 1970;76:499–503.

35. Morales A, Bruce A. The treatment of Peyronie's disease with parathyroid hormone. J Urol. 1975;114:901-2.

36. Bartsch G, Menander-Huber KB, Huber W, Marberger H. Orgotein, a new drug for the treatment of Peyronie's disease. Eur J Rheumatol Inflamm. 1981;4:250-9.

37. Gelbard M, Lindner A, Chvapil M, Kaufman J. Topical beta-aminopropionitrile in the treatment of Peyronie's disease. J Urol. 1983;129:746-8.

38. Gelbard MK, James K, Riach P, Dorey F. Collagenase versus placebo in the treatment of Peyronie's disease: a double-blind study. J Urol. 1993;149:56-8.

39. Puente de la Vega A, Calvo-Mateo M, Domenech M. Laser therapy in Peyronie's disease. Actas Urol Esp. 1985;9:107-9.

40. Strachan Jr, Pryor JP. Prostacyclin in the treatment of painful Peyronie's Disease. Br J Urol. 1988;61:516-7.

41. Bellorofonte C, Ruoppolo M, Tura M. Possibility of using piezoelectric lithtryptor in the treatment of severe cavernous fibrosis. Arch Ital Urol Nefrol Androl. 1989;61:417-22.

42. Benson RJ, Knoll L, Furlow W. Interferon α2β in the treatment of Peyronie's disease. J Urol. 1991;61:1342.

43. Ralph DJ, Brooks MD, Botazzo GF, Pryor JP. The Treatment of Peyronie's disease with tamoxifen. Br J Urol. 1992;70:648-51.

44. Levine LA, Merrick PF, Lee RC. Intralesional verapamil injection for the treatment of Peyronie's disease. J Urol. 1994;151:1522-4.

45. Akkus E, Carrier S, Rehman J, Breza J, Kadioglu A, Lue TF. Is colchicine effective in Peyronie's disease? A pilot study. Urology. 1994;44:291-5.

46. Biagiotti G, Cavallini G. Acetyl-L-carnitine vs tamoxifen in the oral therapy of Peyronie's disease: A preliminary report. Br J U Int. 2001;88:63–7.

47. Scroppo F, Mancini M, Maggi M. Can an external penis stretcher reduce Peyronie's penile curvature? Int J Imp Res. 2001;13(S21): 4th annual meeting of the European Society for Sexual Medicine.

48. Valente EGA, Vernet D, Ferrini MG, Qian A, Rajfer J, Gonzalez-Cadavid NF. L-Arginine and phosphodiesterase (PDE) inhibitors counteract fibrosis in the Peyronie's fibrotic plaque and related fibroblast cultures. Nitric Oxide Biol Chem. 2003;9:229-44.

49. Brant WO, Dean RC, Lue TF. Treatment of Peyronie's disease with oral pentoxifylline. Nat Clin Pract Urol. 2006;3:111-115.

50. *Retracted:* Safarinejad MR. Efficacy and safety of omega-3 for treatment of early-stage Peyronie's disease: A prospective, randomized, double-blind placebo-controlled study. J Sex Med. 2009 Jun;6(6):1743-1754.

51. Soh J, Kawauchi A, Kanemitsu N, et al. Nicardipine vs. saline injection as treatment for Peyronie's disease: a prospective, randomized, single-blind trial. J Sex Med. 2010;7:3743-49.

52. Twidwell J, Levine L. Topical treatment for acute phase Peyronie's disease utilizing a new gel, H-100: a randomized, prospective, placebo-controlled pilot study. Int J Impot Res. 2016; 28:41-5.

53. Polkey H. Induratio penis plastica. Urol Cut Rev. 1928;287-308.

54. Aron E. Le traitement médical de la maladie de Dupuytren par un agent cytostatique (méthylhydrazine). Presse Médical. 1968;76:1956.

55. Sturm M, Lebeuf M. Résultats d'un traitement immunodépresseur dans la maladie de La Peyronie, la maladie de Dupuytren et certaines sclérodermies. Bull de la Société Française de Dermatologie et de Syphiligraphie. 1971;78:523-5.

56. Oosterlinck W, Renders G. Treatment of Peyronie's disease with procarbazine. Br J Urol. 1975;47:219-20.

57. Gelbard MK, Walsh R, Kaufman JJ. Collagenase for Peyronie's disease experimental studies. Urol Res. 1982;10:135-40.

58. Sahbaz A, Aynioglu O, Isik Ha, Ozmen U, Cengil O, Dogan Gun O, Gungorduk K. Bromelain: a natural proteolytic for intra-abdominal adhesion prevention. Int J Surg 2015;14:7-11.

59. Paulis G, Barletta D, Turchi P, Vitarelli A, Dachille G, Fabiani A, et al. Efficacy and safety evaluation of pentoxifylline associated with other antioxidants in medical treatment of Peyronie's disease: a case-control study. Res Rep Urol. 2015 Dec 31;8:1-10.

60. Hu B, Phan SH. Myofibroblasts originate from locally present fibroblasts or from differentiated infiltrating fibrocytes or by local epithelial or endothelial cells. Curr Opin Rheumatol. 2013;25:71-7.

61. Kramann R, DiRocco DP, Humphreys BD. Understanding the origin, activation and regulation of matrix-producing myofibroblasts for treatment of fibrotic disease. J Pathol. 2013;231:273-89.

62. Ding BS, Cao Z, Lis R, et al. Divergent angiocrine signals from vascular niche balance liver regeneration and fibrosis. Nature. 2014;505:97-102.

63. Huang SK, Scruggs AM, McEachin RC, White ES, Peters-Golden M. Lung fibroblasts from patients with idiopathic pulmonary fibrosis exhibit genome-wide differences in

DNA methylation compared to fibroblasts from nonfibrotic lung. PLoS ONE. 2014;9:e107055.

64. Watson CJ, Collier P, Tea I, et al. Hypoxia-induced epigenetic modifications are associated with cardiac tissue fibrosis and the development of a myofibroblast-like phenotype. Hum Mol Genet. 2014;23:2176-88.

65. Dalm V, Dik WA, Thio HB, van den Blink B, van Hagen PM, van Daele PL. Fibrosing disorders: insights into pathogenesis and new treatment options. Ned Tijdschr Geneeskd. 2015;159:A8345.

66. Noble PW, Albera C, Bradford WZ, et al.; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet. 2011;377:1760-9.

67. Richeldi L, du Bois RM, Raghu G, et al.; INPULSIS Trial Investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. N Engl J Med. 2014;370:2071-82.

68. Jang SW, Ihm SH, Choo EH, et al. Imatinib mesylate attenuates myocardial remodeling through inhibition of platelet-derived growth factor and transforming growth factor activation in a rat model of hypertension. Hypertension. 2014;63:1228-34.