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Medical Treatment for Peyronie's Disease: Systematic Review and Network Bayesian Meta-Analysis

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Purpose: To investigate the efficacy of medical treatment options for Peyronie's disease (PD) including oral drugs, intralesional treatment and mechanical treatment compared with placebo treatment using network meta-analysis (NMA).

Materials and Methods: We searched the randomized controlled trials (RCTs) of PD in PubMed, Cochrane library, and EMBASE up to October 2022. RCTs included medical treatment options: oral drugs, intralesional treatment and mechanical treatment. Studies reporting at least one of the outcome measures of interest including curvature degree, plaque size, and structured questionnaires (International Index of Erectile Function, IIEF) were included.

Results: Finally, 24 studies including 1,643 participants met our selection criteria for NMA. There was no statistically significant treatment compared to placebo of the curvature degree, plaque size, IIEF in Bayesian analysis. The SUCRA values of ranking probabilities for each treatment performance, which indicated that hyperthermia device ranked first in NMA. However, in frequentist analysis, 7 of mono treatments (coenzyme Q10 [CoQ10] 300 mg, hyperthermia device, interferon alpha 2b, pentoxifylline 400 mg, propionyl-L-carnitine 1 g, penile traction therapy [PTT], vitamin E 300 mg) and 2 of combination treatments ("PTT–extracorporeal shockwave treatment", "vitamin E 300 mg–propionyl-L-carnitine 1 g") were statistically significant for improvement of curvature degree, and 9 of mono treatments (CoQ10 300 mg, hyaluronic acid 16 mg, hyperthermia device, interferon alpha 2b, pentoxifylline 400 mg, propionyl-L-carnitine 1 g, verapamil 10 mg, vitamin E 300 mg, vitamin E 400 U) and 3 of combination treatments ("interferon alpha 2b–vitamin E 400 U", "verapamil 10 mg–antioxidants", "vitamin E 300 mg–propionyl-L-carnitine 1 g") were statistically significant in the improvement of plaque size.

Conclusions: At present, there is no clinical treatment alternatives that have been demonstrated to be effective compared to placebo. Nonetheless, as the frequentist approach has shown that a number of agents are efficacious, further research is expected to develop more effective treatment options.

Keywords: Administration, topical; Erectile dysfunction; Oral medicine; Penile induration; Practice management

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The World Journal of MEN's HEALTH

INTRODUCTION

A frequently arising psychosexual disorder, Peyronie's disease (PD) typically presents with discomfort, curvature and or/deformity of the penis in association with palpable plaque(s) and erectile dysfunction (ED) [1]. The condition generally tends to become more severe over time, a situation that is evident in over 50% of patients without therapeutic intervention [2]. A number of factors are likely to contribute to the pathophysiological mechanisms underlying PD [1], although one possible etiology for the development of penile plaques is recurring injury to an erect penis [3,4]. The latter disturbs the structure of the tunica albuginea; this is associated with the liberation of a range of cytokines and growth factors, e.g. transforming growth factor (TGF)-β1. Macrophage and fibroblast replication additionally arise which lead to surplus fibrin and collagen being laid down [5], and ultimately, disarray of the extracellular matrix and cell shrinkage. Fibroblasts dedifferentiate into myofibroblasts, thus precipitating the development of fibrous plaques between the strata of the tunica [6]. Remodeling of plaques and distortion of penile morphology may be hastened by matrix metalloproteinases and their tissue inhibiting factors [7].

To date, there is little known about the exact mechanisms underlying PD and the associated fibrotic conditions. TGF-β has been recognized as a key contributor to fibrotic change, but the latter process includes numerous pathways, together with an abundance of mediating cytokines and growth factors, many of which are yet to be delineated in patients with PD. A broad spectrum of management strategies is employed in patients with PD. Although clinical recommendations have been published, the therapeutic options selected are mainly governed by the experiences and knowledge of the treating doctor [1]. Despite the existence of a number of systematic reviews which describe the efficacy of drug therapies, no analyses have yet been published which evaluate the general results of the more conservative options, which include oral, intralesional and mechanical types of treatment. These options are essential as these are advised by the published treatment recommendations in the first instance, except where the patient expresses a desire for a more long-term solution and is willing to take the risk associated with operative reconstructive techniques [8,9]. Russo et al [10] reported that *Clostridium histolyticum* and interferon alpha 2b showed the best outcome in terms of penile curvature, whereas hyaluronic acid was most efficient in relation to erectile function in the meta-analysis comparing all available intralesional treatment for PD. Bakr and El-Sakka [11] reported extracorporeal shockwave treatment (ESWT) fails to improve penile curvature or pain in men with PD, although ESWT may reduce plaque size. Pyrgidis et al [12] reported the result of available combination treatment modalities in their randomized or observational comparative studies assessing any conservative combination therapies for PD.

The aim of the current review is to investigate the clinical treatment choices available. These encompass oral, intralesional and mechanical types of treatment, and their effectiveness is judged against the use of a placebo.

MATERIALS AND METHODS

We registered the study protocol in the PROSPERO database (registration number CRD42022372906). The study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [13].

The PRISMA Checklist are included as a Supplement Materials. The inclusion criteria were defined using the population, intervention, control, and outcome (PICO) method (Supplement Table 1).

1. Data sources and literature searches

We searched the PubMed and Cochrane library using the MeSH (Medical Subject Headings terms) and text keywords to identify reports published up to October 2022. We included all full-text publications reporting the outcomes of randomized controlled trials (RCTs) in PD patients treated with medical treatment including oral drug, injectional therapy, and mechanical therapy. Studies reporting at least one of the outcome measures of interest including curvature degree, plaque size, and structured questionnaires (International Index of Erectile Function, IIEF) were included in the meta-analysis.

The subject headings and text keywords included those related to the population (male patients with PD), interventions & comparisons (15 mono treatment): (1) oral drug (colchicine, colchicine 1 mg, coenzyme Q10 [CoQ10] 300 mg, vitamin E 400 U, vitamin E 300 mg, pentoxifylline 400 mg, propionyl-L-carnitine 1 g, vera-

pamil 10 mg, and antioxidants); (2) injectional therapy (collagenase clostridium histolyticum [CCH], hyaluronic acid 16 mg, and interferon alpha 2b); (3) mechanical therapy (ESWT, hyperthermia device, penile traction therapy [PTT]) and 4 combination treatment ("interferon alpha 2b–vitamin E 400 U", "vitamin E 300 mg–propionyl-L-carnitine 1 g", "PTT–ESWT", and "verapamil 10 mg–antioxidants"). The search terms were grouped according to Boolean operators (AND, OR, NOT). The same search strategy was adopted for EMBASE using Emtree (EMBASE subject headings). Additional studies were screened by two independent investigators (SR Shim and JH Kim) through manual search of clinical trial databases and our search strategy is provided in Supplement Table 1.

2. Inclusion and exclusion criteria for study selection

The inclusion criteria for relevant studies were as follows: (1) patients with a diagnosis of with PD; (2) the outcome was curvature degree, plaque size, and IIEF; (3) duplicated publications were excluded, as were publications that did not contain original data, such as review articles, case reports, conference abstracts, editorials, letters, and guidelines; (4) human-based RCTs rather than cross-over design. Exclusion criteria were as follow: (1) non-human RCTs and (2) no comparison groups (3) surgical treatment. Two investigators (SR Shim and JH Kim) performed an independent initial screening by title and abstracts of all the articles using the predefined inclusion criteria. All of the researchers independently reviewed the full-text articles to see if they met the inclusion criteria. Furthermore, the same authors independently extracted data using a data extraction form. The final inclusion of each article was determined by all investigators through evaluation and discussion. To ensure the integrity of the meta-analysis and the absence of overlapping data, the references and data for each included study were cross-checked. Disagreements were resolved via consensus among the co-authors.

3. Data extraction and measurement outcomes

Details of the basic study information (first author, publication year, country, and follow-up period), patient characteristics (number of patients and age range), and technical aspects (inclusion & exclusion criteria, and treatments) were extracted from the included articles, using a predefined data extraction form. In one study, when there were several treatment durations, the effect size was calculated in the last part, and if there were several dose ranges, the highest dose was set, and the dose was converted based on daily dosage. Only studies providing complete information were included in the final meta-analysis.

4. Data analysis

For Bayesian network meta-analysis (NMA), specific graphical analysis was completed using the "gemtc" package in R software v.4.2.1 (R Foundation for Statistical Computing). Analyses according to previously described technical implementation of the Bayesian method using R software was performed. First, a prior distribution and the likelihood were calculated from the present data, and a Bayesian hierarchical model was created in NMA. Second, after Markov chain Monte Carlo (MCMC) simulation, and a distribution that best converges the posterior distribution was set. The probability of stable distribution and the area under the posterior distribution function were determined through the MCMC simulation. Finally, statistical reasoning for the treatment effect was performed with the determined posterior distribution. Therefore, the Bayesian NMA was used to analyze the posterior distribution, even though it is not a standard distribution generally used in statistics. Particularly for the MCMC simulation, we selected the random effect model that had four chains, 5,000 burn-ins, 30,000 iterations, and an interval of 5 to sufficiently remove the effect of initial values, increase the iterations and extraction interval, and minimize the MCMC error and the deviance information criterion variation with almost no variations and stability of various plots. For additional analysis, we also conducted a frequentist NMA based on a graph-theoretical approach using the "netmeta" package.

For consistency assumption of NMA, we performed node-splitting assessments to determine the association between the direct and indirect treatment comparisons. The surface under the cumulative ranking curve (SUCRA) was used to calculate the probability of each treatment being the most effective method based on a Bayesian approach using probability values to facilitate interpretation of treatment performance; the larger the SUCRA value was, the higher the rank of

The World Journal of MEN's HEALTH

the intervention [14,15]

The analysis pooled the mean difference (curvature degree and IIEF) and standardized mean difference (plaque size) and 95% credible intervals (CrI). A two-sided p value of <0.05 was considered statistically significant. We assessed publication bias (or small-study effects) using a funnel plot. We also used the Egger test (i.e., linear regression test of funnel plot asymmetry) when assessing the publication bias.

5. Quality assessment

The Cochrane Collaboration risk-of-bias 2.0 tool was used to assess the risk of bias and methodological quality. We evaluated five parameters: 1) randomization process; 2) deviations from the intended interventions; 3) missing outcome data; 4) measurement of the outcome; and 5) selection of the reported result. Each domain was assigned a risk of bias rating of high, low, or unclear. The overall risk of bias was considered to be low if all domains were rated as "Low," some concerns if even one domain was rated as "Some concerns," and high risk if even one domain was rated as "High," or more than two domains were received the "Some concerns" [16,17].

RESULTS

1. Study selection

The initial search identified a total of 217 articles from electronic databases (PubMed, 53; Cochrane, 54; EMBASE, 10), of which 95 were unrelated to the topic, contained overlapping data, or appeared in more than one database and were excluded. After a more detailed review, an additional 56 papers that were not adequate publication type were eliminated. After full-text assessments, 66 studies were eligible for full-text review. Of these, 42 were further excluded for the following reasons: not RCT (n=9), not treatment for PD (n=6), not PD (n=3), no quantitative outcome (n=13), editorial comment (n=1), IRB submission paper (n=1), not enough sample size (n=4), not English (n=5) (Fig. 1, Table 1). Finally, 24 studies including 1,643 participants met our selection criteria for NMA, among which 2-arm, 3-arm, and 4-arm studies were 12, 1, and 1 (Fig. 2).

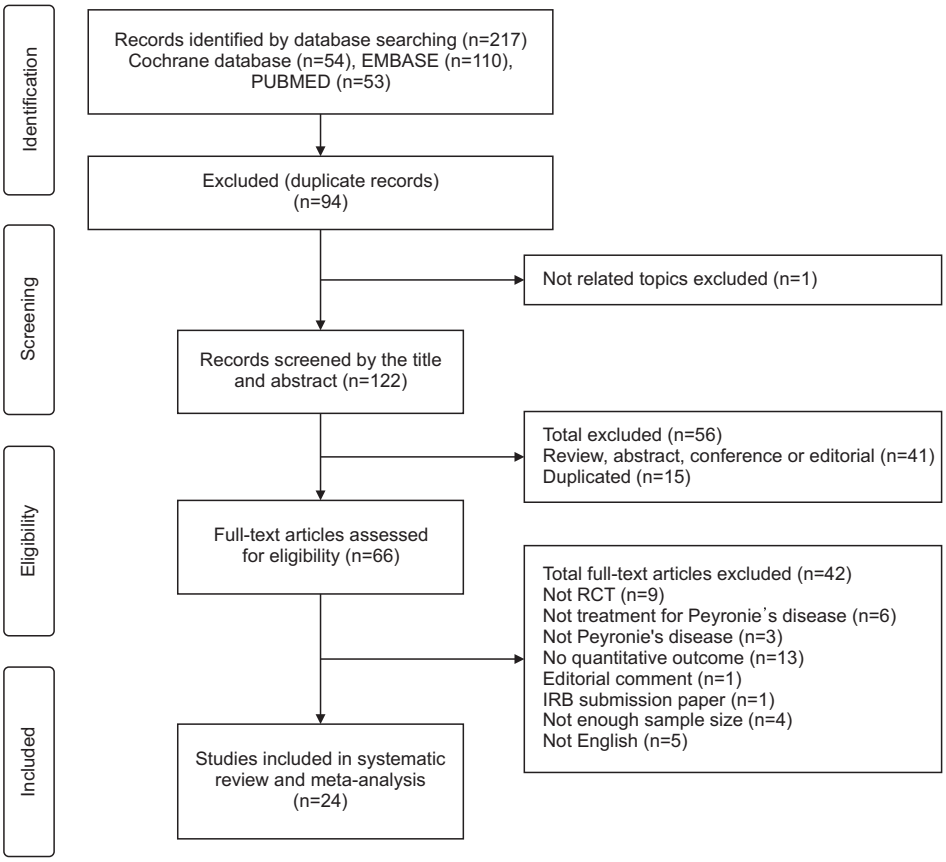

Fig. 1. Flow diagram. RCT: randomized controlled trial.

Table 1. Characteristics of all studies included in meta-analysis

Author (year)	Journal	Country	No. of patients	Subject description		Experimental description	
				Inclusion criteria	Exclusion criteria	Treatment	F/U duration
Rehman et al (1998) [1]	Urology	United States	14	35–70 years, previous discontinuation of medication for PD at least 3 months	Oral calcium antagonist	Placebo Verapanil 10 mg injection once a week	3 months
Safarinejad (2004) [2]	Int J Impot Res	Iran	84	PD	All medical therapy within 8 weeks	Placebo Oral colchicine 1 mg daily	4 months
Perugia et al (2005) [3]	Int J Hyperthermia	Italy	60	Advanced PD with pain during intercourse, penile curvature affecting vaginal penetration and/or ED	Taking PDE-5 inhibitor, history of PD treatment	Local hyperthermia device (FLEXITERM CX 2000) Twice a week Single injection of verapamil 10 mg (1 mg/cc)	6 months
Kendirci et al (2005) [4]	J Sex Med	United States	39	Age ≥18 years, PD >12 month, penile curvature <30 degrees on erection		Placebo (normal saline 10 mL) injection per week Interferon α2b 5×10^6 unit+normal saline 10 mL injection per week	12 weeks
Inal et al (2006) [5]	Urology	Turkey	30	Early stage of PD within 6 months	History of penile surgery, pelvic trauma, medication for PD	Interferon-α2b 5MU injection Oral vitamin E 400 U twice daily Interferon-α2b 5MU injection+oral vitamin E 400 U twice daily	12 weeks
Cavallini et al (2007) [6]	Urology	Italy	77	Chronic PD patients	PSA >4 mg/mL, medical treatment for PD or ED, recurrent PD, hormonal abnormality, pelvic surgery history, myocardial or cerebral ischemia within 6 mo., major surgery, alcohol or tobacco abuse, untreated diabetes, hypertension or hypotension	Verapamil 10 mg+normal saline 4 mL injection once in 2 weeks Verapamil 10 mg+normal saline 10 mL injection once in 2 weeks Veraamil 10 mg+normal saline 20 mL injection once in 2 weeks	24 weeks
Greenfield et al (2007) [7]	J Urol	United States	42	PD patients	Verapamil injection l therapy for PD, ventral plaque, extensive plaque calcification	Normal saline 4 cc injection+electropromotive device twice a week Verapamil 10 mg/NS 4 cc injection+electropromotive device twice a week	3 months
Safarinejad et al (2007) [8]	J Urol	Iran	274	Primary PD, onset more than 12 months	Organic cause of PD	Placebo Oral vitamin E 300 mg twice daily Oral propionyl-L-carnitine 1 g twice daily Oral vitamin E 300 mg+Oral propionyl-L-carnitine 1 g twice daily	6 months

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Table 1. Continued 1

Author (year)	Journal	Country	No. of patients	Subject description		Experimental description	
				Inclusion criteria	Exclusion criteria	Treatment	F/U duration
Palmieri et al (2009) [9]	Eur Urol	Italy	100	Age between 18–75 years, only one plaque with maximum size of 3.75 cm^2, no previous medical or surgical therapies for PD, stable sexual relationship, painful erection with VAS ≥5, ED, penis recurvatum	Blood coagulation disorder, cardiac pacemaker, lower urinary infection, vascular disorder in the path of the shock waves	Placebo ESWT	24 weeks
Chitale et al (2010) [10]	BJU Int	United Kingdom	36	Stable PD over 6 months, age >18 years, palpable plaque along the penis with deformity	Congenital curvature of the penis, previous treatment for PD (surgical/medical), on wafarin, patient with total ED in need of therapy for ED	Placebo (sham treatment) Shock wave therapy	6 months
Safarinejad (2010) [11]	Int J Impot Res	Iran	186	18–60 years, at least 2 previous failed medical treatment for PD, reported ED with painful penile curvature at least 12 months, presence of ED without any obvious organic causes other than PD, presence of penile plaque with a maximum size of 2 cm^2, stable sexual relationship, presence of painful erection and penile recurvatum	Other sexual dysfunction, absence of penile curvature, history of penile surgery or pelvic trauma, endocrinopathy, serum creatinine >1.8 mg/100 mL, alcohol or tobacco use, supplemenation with vitamins or traditional herb in previous 3 mo, therapies interfering with CoQ10 such as antioxidants	Placebo Oral CoQ10 300 mg once daily	24 weeks
Safarinejad et al (2010) [12]	BJU Int	Iran	228	Early chronic PD, history of ≥12 months, previous treatment of PD, presence of ED as IIEF <26, no history of penile surgery or pelvic trauma	Medical treatment for sexual dysfunction, recurrent PD, endocrinopathy, serum creatinine >1.8 mg/100 mL, chronic liver disease, alcohol or tobacco use, age >60 years, supplementation of vitamins or traditional herb in previous 3mo., therapies interfering with pentoxifylline	Placebo Pentoxifylline 400 mg twice daily	6 months
Mehrsai et al (2013) [13]	Andrology	Iran	30	Disease period <2 years, presence of pain on erection, penile deviation <45 degree, ability to perform vaginal intercourse	Calcified plaque, ED referable to psychological, neurological, hormonal or vascular causes, contraindication to the use of verapamil of dexamethasone, history of diabetes, congenital penile curvature or chordee with hypospadias	10 mg verapamil+4 mg dexamethasone+2 mL distilled water with TEA weekly 10 mg verapamil+4 mg dexamethasone+2 mL distilled water with intralesional injection weekly	3 months

Table 1. Continued 2

Author (year)	Journal	Country	No. of patients	Subject description		Experimental description	
				Inclusion criteria	Exclusion criteria	Treatment	F/U duration
Favilla et al (2014) [14]	Andrologia	Italy	113	Acute phase of PD	Previous medical or surgical treatment for PD, IIEF-5 score <22, any medical treatment for sexual dysfunction before or during the study, stabilized PD symptoms (>12 mo), completely calcified plaques at USG, congenital penile curvature or chordee with hypospodias, age >75 yr, coagulation disorders or severe cardiovascular disease, hypogonadism	Verapamil 10 mg+5 mL saline, intralesional injection weekly for 12 weeks Verapamil 10 mg+5 mL saline, intralesional injection weekly for 12 weeks, oral antioxidants once daily	3 months
Ozturk et al (2014) [15]	Ir J Med Sci	Turkey	39	Primary PD with no longer than 6 months, non-calcified plaque	Previous treatment for PD or ED, hormonal abnormality, alcohol or tobacco abuse, hypertension, coronary artery disease, diabetes	Oral vitamin E 400 IU daily sildenafil 50 mg daily	12 weeks
Toscano et al (2016) [16]	Int Braz J Urol	Brazil	25	PD patient	Penile trauma, PD with longer than 18months, medical or surgical treatment history for PD, history of using colchicine or verapamil within 3 months	Thiocolchicine 4 mg+2 mL saline intralesional injection weekly Verapamil 5 mg+2 mL saline intralesional injection weekly	7 weeks
Favilla et al (2017) [17]	Andrology	Italy	132	Age >18 years, IIEF-5 score >11, acute phase of PD	chronic or fibrotic phase of PD, previous medical or surgical or EWST treatment for PD, calcified plaque or hourglass deformity as defined at USG, IIEF score <7, any medical treatment for ED before or during study, severe penile curvature incompatible with sexual intercourse	Verapamil 10 mg+5 mL saline intralesional injection weekly Hyaluronic acid 16 mg/2 mL injection weekly	12 weeks
Ralph et al (2017) [18]	J Sex Med	Egypt	30	Age ≥18 years, stable symptomatic PD	Penile curvature <30 degree or >90 degree, hourglass deformity, compromised penile hemodynamics, significant ED that failed to respond to oral PDE-5 inhibitor, priapism history, calcified plaque, previous medical treatment for PD within 3months, previous surgery for PD	Collagenase *clostridium histolyticum* 0.58 mg injection+vacuum-pump therapy+plaque modeling Collagenase *clostridium histolyticum* 0.58 mg injection+vacuum-pump therapy	36 weeks

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Table 1. Continued 3

Author (year)	Journal	Country	No. of patients	Subject description		Experimental description	
				Inclusion criteria	Exclusion criteria	Treatment	F/U duration
Alom et al (2019) [19]	J Sex Med	United States	113	PD with >30 degree curvature	Previous PD therapies, plaque calcification, hourglass deformities, multiplanar curvature	0.9 mg Collagenase *clostridium histolyticum* injections 0.9 mg Collagenase *clostridium histolyticum* injections+penile traction therapy (other device) 0.9 mg Collagenase *clostridium histolyticum* injections+penile traction therapy (RestoreX device)	24 weeks
Ziegelmann et al (2019) [20]	J Urol	United States	110	Age ≥18 years with PD	Penile curvature <30 degrees, stretched penile length <7 cm, diabetes with end-organ failure, ED unresponsive to PDE-5 inhibitor or penile injection	Placebo (no treatment) Penile traction therapy with Restore X device daily	3 months
Joseph et al (2020) [21]	J Sex Med	United States	64	Age ≥18 years with PD	Penile curvature <30 degrees, stretched penile length <7 cm, diabetes with end-organ failure, ED unresponsive to PDE-5 inhibitor or penile injection	Penile traction therapy to penile traction therapy placebo to penile traction therapy with Restore X device daily	3 months
Cai et al (2021) [22]	World J Mens Health	Italy	81	Age >18 years, acute phase of PD, IIEF score >11	Allergy to study medication, reluctance to penile injection, previous treatment for PD	Hyaluronic acid 150 mg PO per 48 h+hyaluronic acid intralesional injection (16 mg/2 mL) per week Hyaluronic acid intralesional injection (16 mg/2 mL) per week	6 weeks
Mortensen et al (2021) [23]	Res Rep Urol	Denmark	30	Age with 18–80 years, diagnosed with PD more than 6 months, stable phase of PD, penile curvature 20–90 degrees	Previous penile surgery or ESWT treatment	Vacuum pump+sham ESWT Vacuum pump+ESWT once a week for 5 weeks	6 months
Chung and Wang (2022) [24]	Investig Clin Urol	Australia	50	Age ≥18 years, stable PD(penile deformity unchanged for 6 months), failed oral therapy, presence of palpable plaque, single axis penile curvature(<90 degree)	Presence of hinge or lateral indentation or hourglass deformity, previous surgical treatment for PD, IIEF-15 score ≤16	Verapamil 10 mg+saline 4 mL intralesional injection Collagenase *clostridium histolyticum* 0.58 mg injection+0.5 mL saline intralesional injection	24 months

All references in Table 1 are available in the Supplement Material.

F/U: follow-up, PD: Peyronie`s disease, ED: erectile dysfunction, PDE-5 inhibitor: phosphodiesterase-5 inhibitor, PSA: prostate specific antigen, VAS: visual analogue scale, ESWT: extracorporeal shock wave therapy, TEA: transdermal electromotive administration, IIEF: International Index of Erectile Function, USG: ultrasonography.

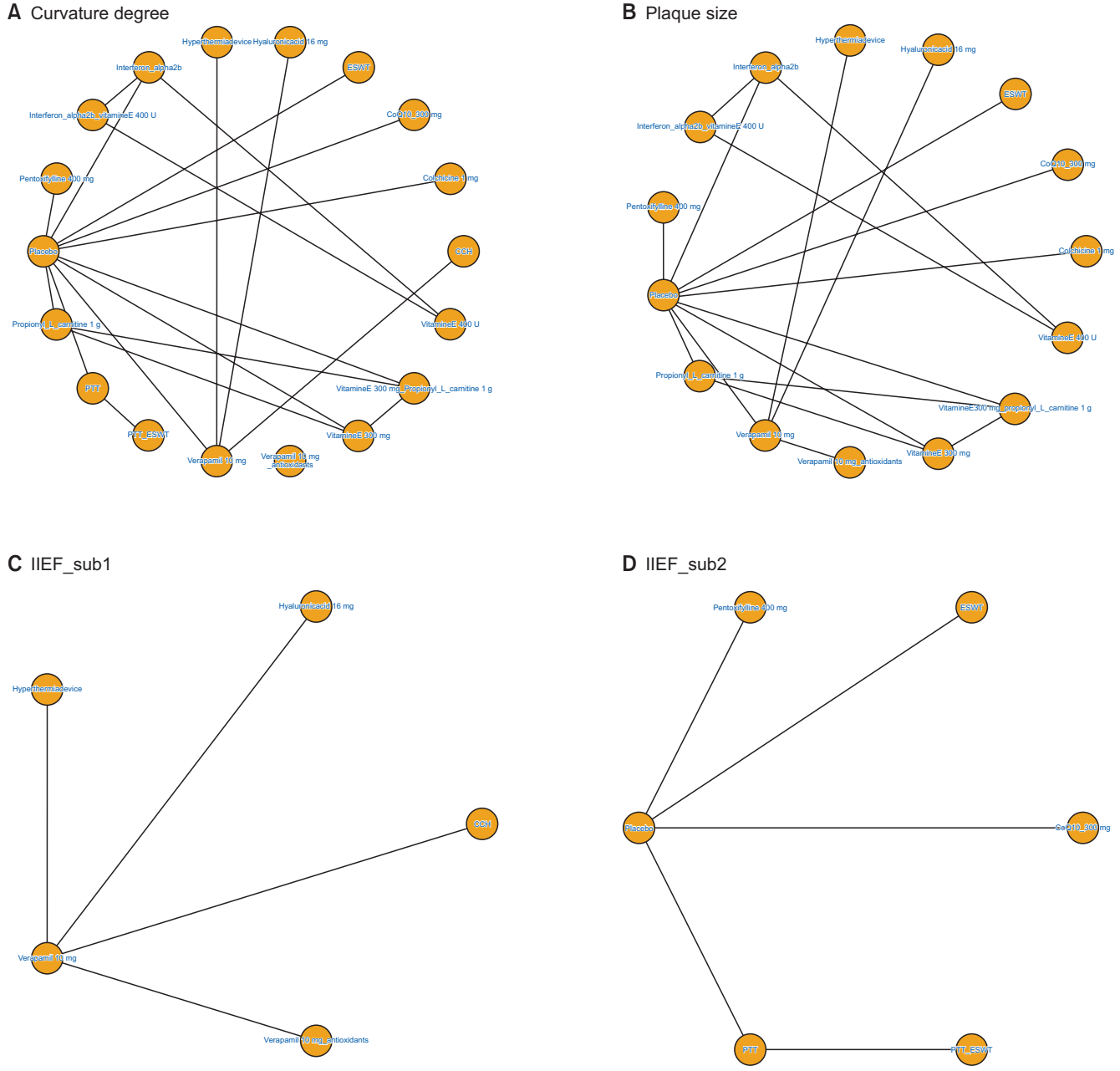


Fig. 2. Network plot. (A) Curvature dgree, (B) plaque size, (C) IIEF_sub network 1, (D) IIEF_sub network 2. IIEF: International Index of Erectile Function, PTT: penile traction therapy, ESWT: extracorporeal shockwave treatment, CCH: collagenase clostridium histolyticum, CoQ10: coenzyme Q10.

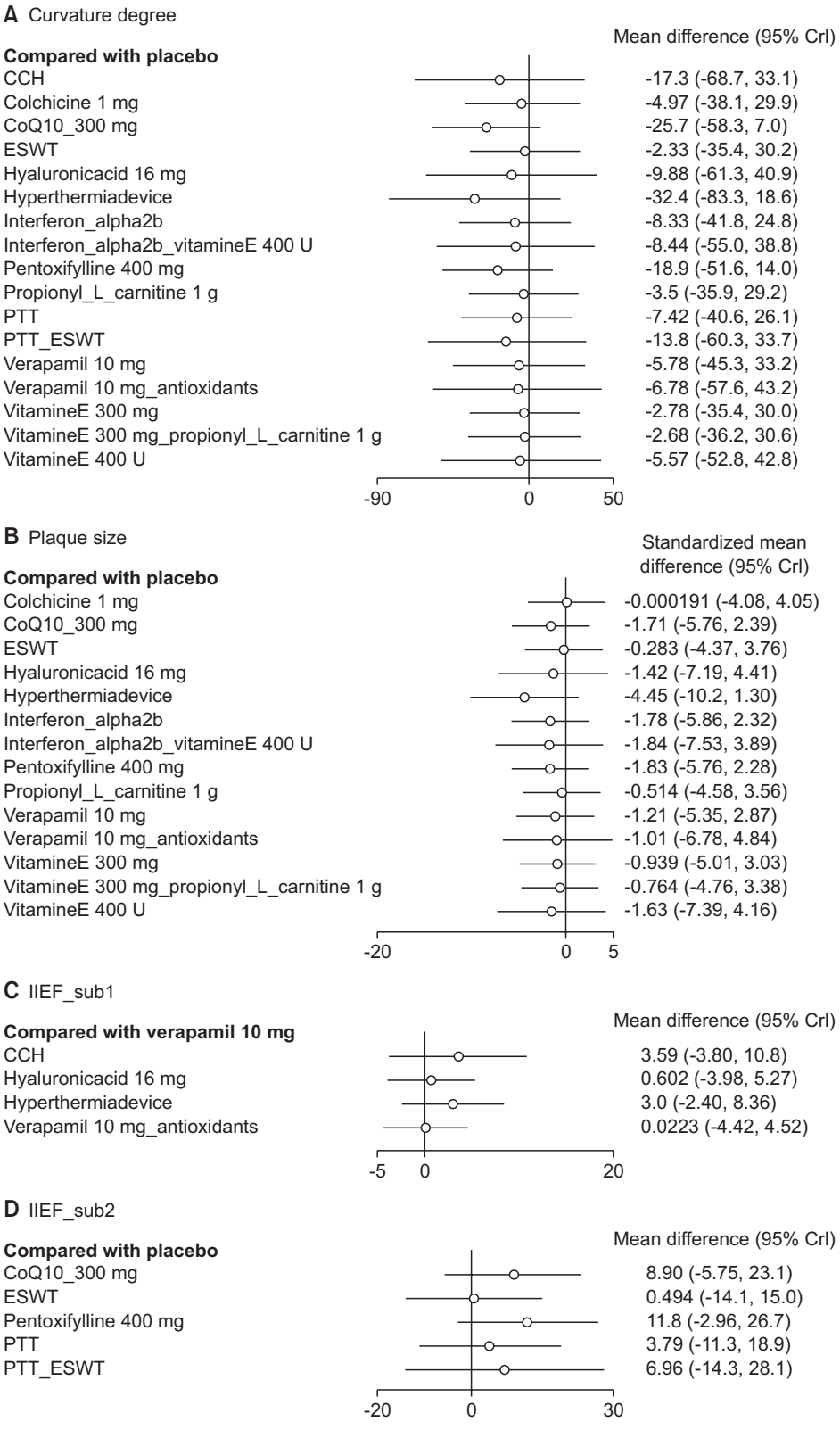
2. Quality assessment

We evaluated the twenty-four PD studies using the five RoB 2 domains to determine the risk of bias for the included studies. In D1, one study was classified as "High". In D2, four studies and one study were classified as "Some concerns" and "No information." In D3, four studies were classified as "Some concerns." In D4 and D5, all studies were classified as "Low" or "Some concerns." Based on these evaluations, the overall risk of bias was ranked. Fourteen studies were classified as "Low," six studies as "Some concerns," and four studies as "High" (Supplement Fig. 1).

3. Outcomes

In curvature degree, a total of 1,643 patients from 14 direct comparison trials were included 21 effect sizes with 18 treatments. There was no statistically significant treatment compared to placebo in Bayesian analysis. Of these, 7 of mono treatments (CoQ10 300 mg, hyperthermia device, interferon alpha 2b, pentoxi-

fylline 400 mg, propionyl-L-carnitine 1 g, PTT, vitamin E 300 mg) and 2 of combination treatments ("PTT–ESWT", "vitamin E 300 mg–propionyl-L-carnitine 1 g") were statistically significant in frequentist NMA. The pooled overall mean differences of curvature degree were -32.500 (95% CrI: -52.245, -7.755) in hyperthermia



Fig, 3. Network meta-analysis forest plot. (A) Curvature dgree, (B) plaque size, (C) IIEF_sub network 1, (D) IIEF_sub network 2. IIEF: International Index of Erectile Function, PTT: penile traction therapy, ESWT: extracorporeal shockwave treatment, CCH: collagenase clostridium histolyticum, CoQ10: coenzyme Q10, CrI: credible intervals.

device, -25.700 (95% CrI: -26.866, -24.534) in CoQ10 300 mg, -18.900 (95% CrI: -20.004, -17.796) in pentoxifylline 400 mg (Fig. 3 and Supplement Fig. 2).

In plaque size, a total of 1,398 patients from 11 direct comparison trials were included 18 effect sizes with 15 treatments. There was no statistically significant treatment compared to placebo in Bayesian analysis. Of these, 9 of mono treatments (CoQ10 300 mg, hyaluronic acid 16 mg, hyperthermia device, interferon alpha 2b, pentoxifylline 400 mg, propionyl-L-carnitine 1 g, verapamil 10 mg, vitamin E 300 mg, vitamin E 400 U) and 3 of combination treatments ("interferon alpha 2b–vitamin E 400 U", "verapamil 10 mg–antioxidants", "vitamin E 300 mg–propionyl-L-carnitine 1g") were statistically significant in frequentist NMA. The pooled overall standardized mean differences of plaque size were -4.486 (95% CrI: -5.865, -3.108) in hyperthermia device, -1.850 (95% CrI: -3.000, -0.701) in "interferon alpha 2b–vitamin E 400 U", -1.832 (95% CrI: -2.142, -1.523) in pentoxifylline 400 mg (Fig. 3, Supplement Fig. 2).

In IIEF, a total of 1,271 patients from 4 direct comparison trials (CCH, hyaluronic acid 16 mg, hyperther-

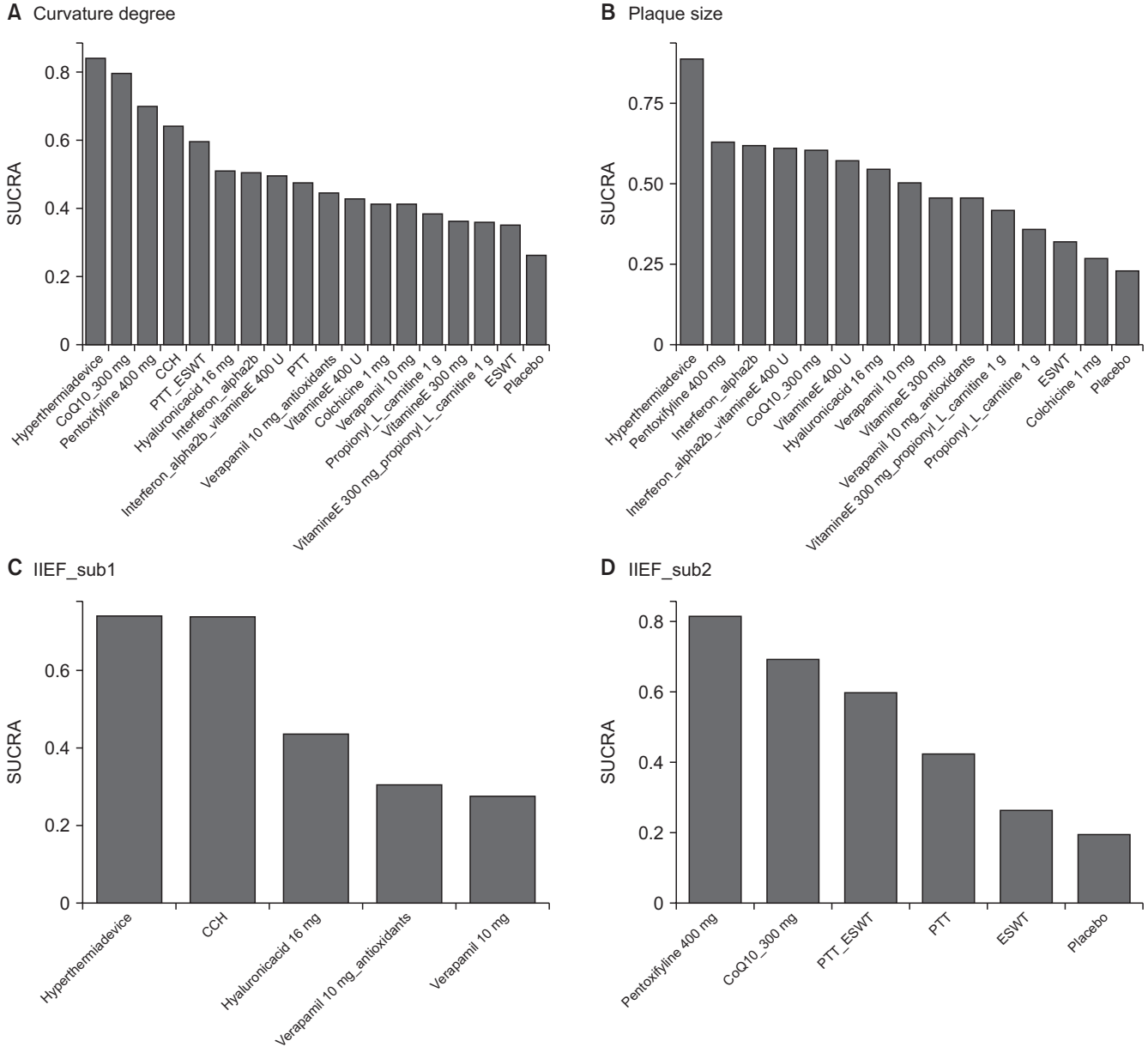


Fig. 4. SUCRA (surface under the cumulative ranking curve probabilities). (A) Curvature dgree; (B) plaque size; (C) IIEF_sub network 1; (D) IIEF_sub network 2. IIEF: International Index of Erectile Function, PTT: penile traction therapy, ESWT: extracorporeal shockwave treatment, CCH: collagenase clostridium histolyticum, CoQ10: coenzyme Q10.

The World Journal of MEN's HEALTH

mia device, verapamil 10 mg, "verapamil 10 mg–antioxidants") and 5 direct comparison trials (CoQ10 300 mg, pentoxifylline 400 mg, placebo, ESWT, PTT, PTT–ESWT) were two separated treatment network groups, thus we approached for each treatment groups. There was no statistically significant in Bayesian analysis. Of these, 3 of mono treatments (CoQ10 300 mg, pentoxifylline 400 mg, PTT) and 1 of combination treatments ("PTT–ESWT") was statistically significant in frequentist NMA. The pooled overall mean differences of IIEF were 11.700 (95% CrI: 8.788, 14.612) in pentoxifylline 400 mg, 8.900 (95% CrI: 8.331, 9.469) in CoQ10 300 mg, 7.030 (95% CrI: 2.817, 11.243) in PTT_ESWT (Fig. 3, Supplement Fig. 2).

Fig. 4 shows the SUCRA values of ranking probabilities for each treatment performance, which indicated that hyperthermia device ranked first in NMA.

4. Inconsistency test

The inconsistency tests for NMA assumption were analyzed using the node-splitting method, and the results indicated consistency among the direct and indirect evidence of all outcomes. Therefore, a consistency model was applied in the current study (all p>0·05).

5. Publication bias

The statistical approaches for the detection of publication bias or small-study effect in fifty-nine studies are shown in Supplement Fig. 3. Egger's regression (two-tailed p=0.795) and a visual inspection of symmetry graphic in the funnel plot suggested that there was no evidence of publication bias or small-study effect in this NMA.

DISCUSSION

The potential efficacy of all the investigated therapeutic alternatives was demonstrated in the current study in comparison to a placebo, using a Bayesian analytical technique. A frequentist approach demonstrated that, when judged against a placebo, a number of treatments led to an attenuation of penile curvature and plaque dimensions (Supplement Materials). The Bayesian technique was utilized and acknowledged as it had greater robustness than the frequentist approach, especially in the presence of a low study number. A positive likelihood of a remedial effect was established. Nevertheless, as pharmaceutical agents were determined to exhibit efficacy through the frequentist approach, it is anticipated that more efficacious treatments will undergo innovation after additional research has been performed.

The complicated mechanisms underlying PD form the principal hindrance to the lack of currently applicable standard treatment. It has been established that a number of key processes relating to extracellular inflammatory and fibrotic reaction mediators are involved in PD, although numerous pathways within the cells have yet to be fully delineated. The TGF-β pathway has been recognized as a major actor in the development of fibrosis [18]. The TGF-β is an early mediator produced in response to cell damage and stimulates myoblast proliferation and collagen production. This process is known to be involved in PD from the animal study [19]. TGF-β also inhibits production of mediators involved in collagenolysis and fibrinolysis, resulting in excess collagen deposition within the ECM, which then leads to plaque formation in PD [20]. TGF-β can also increase production of reactive oxygen species, and has been implicated in plaque calcification through osteoblast differentiation [21]. In addition to TGF-β, other cytokines have been implicated in the pathogenesis of PD. Some of the pro-inflammatory cytokines involved in PD include interleukin-1 (IL-1), IL-2 β, IL-6, IL-8, tumor necrosis factor-alpha, connective tissue growth factor, and others [22]. However, molecular pathways associated with fibrosis within specific viscera have not yet been described in penile tissue [23,24]. Previous research at the intracellular molecular level in PD has generally centered on the TGF-β pathway, but gaining additional comprehension of alternative mechanisms that trigger fibrotic change could facilitate the presentation of de novo therapeutic targets in patients with PD.

Therapeutic goals in PD include promoting erectile function and lack of sexual discomfort; this is achieved by endeavoring to slow advancement of the pathology and to diminish plaque formation and the curvature of the penis. Presently available treatments encompass drugs, which are generally indicated early in the pathology, minimally invasive options, e.g., CCH, and corrective surgery, which is only indicated once the pathology becomes stable. The efficiency of CCH has been substantiated by high-level evidence, although no difference in effectiveness to a placebo was found in the current study.

The clinical endpoint triad selected in this review comprised the degree of penile curvature, plaque dimensions and international index of erective function. No efficacy in relation to these endpoints was determined following therapy using the Bayesian approach, but the frequentist method indicated that, *versus* a placebo, a number of therapeutic options for PD led to a reduction in penile curvature and plaque measurements (Supplement Materials).

The Bayesian method generated an ordered treatment ranking of mechanical therapy, CoQ10, pentoxifylline given orally and CCH (Fig. 4). Despite the fact that this analytical strategy failed to indicate the efficacy of the therapeutic choices compared to a placebo in PD, the frequentist method highlighted a number of treatments deemed to be effective, i.e. mechanical treatment, CoQ10, oral pentoxifylline and interferon alpha 2b (Supplement Fig. 2).

The evidence to support mechanical therapy iontophoresis or transdermal electromotive pharmaceutical agent delivery remains unsubstantiated and so the potential use of these options in patients with PD merits additional research [1,2]. The energy transferred to the tunica rather than the immediate actions of the medication per se may account for the curvature decrease seen. There are few adverse events associated with iontophoresis, although the dispersive electrodes may induce temporary dermal reddening. The length of the penis can be enhanced, and deformity and discomfort diminished by PTT [25]. The frequentist method employed in the current study demonstrated that in contrast to a placebo, patients with PD received benefits from mechanical treatments, such as a hyperthermal device, and mechanical treatment with PTT together with ESWT. The same analysis method indicated that pentoxifylline was also efficacious against a placebo as a therapeutic option in PD.

Pentoxifylline and colchicine, in combination with PTT, forms an expedient treatment option which is cheap and efficacious for the penile distortion and plaque relating to PD [26]. Pentoxifylline has been demonstrated in fibroblasts derived from the tunica albuginea *in vitro* to promote collagen metabolism, to diminish fibrous tissue formation and to restrict elastogenesis [27]. In the current study, the frequentist method demonstrated the effectiveness of pentoxifylline against placebo.

A fat-soluble, vitamin-like quinone, which is the sole lipid-soluble antioxidant produced endogenously, CoQ10 (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone, and also referred to as ubiquinone or ubidecarenone) undergoes reduction via a semiubiquinone radical, CoQ10H, to form ubiquinole (CoQ10H2) [28]. In pathologies linked with oxidative stress, diminished serum CoQ10 titers [29] and a reduced CoQ10H2:CoQ10 ratio [30] have been detected. Treatment with CoQ10 in early stage ongoing PD diminishes the dimensions of the plaque and relieves penile curvature. The frequentist method indicated that compared with a placebo, CoQ10 appeared effective as a therapeutic option in PD.

Interferon is a protein of a low molecular weight. Its effects as a modulatory factor on the immune response via a spectrum of anti-proliferative mechanisms is well-established; an equilibrium of pro- and anti-inflammatory agent expression is achieved through interferon alpha-2b. The latter, administered as either a lone agent or together with PTT, led to a modest reduction in penile curvature when compared with the use of a placebo.

Pyrgidis et al [12] reported the result of available combination treatment modalities including the addition of adjunctive mechanical therapies to CCH, do not improve symptoms further compared with monotherapy and should not be implemented in patients with active or stable PD. Our findings indicate that 2 of combination treatments ("PTT–ESWT", "vitamin E 300 mg–propionyl-L-carnitine 1 g") in penile curvature, 3 of combination treatments ("interferon alpha 2b–vitamin E 400 U", "verapamil 10 mg–antioxidants", "vitamin E 300 mg–propionyl-L-carnitine 1 g") and combination treatments ("PTT–ESWT") in IIEF were statistically significant in frequentist NMA. Combination treatment has emerged as a promising treatment modality when monotherapy alone is less effective. Regenerative medicine represents a novel therapy for the treatment of PD using mesenchymal stem cell therapy with both curative and preventive potential [31]. Stem cells can be used in tissue engineering to repair a disrupted process [32]. Several studies have demonstrated the efficacy of stem cell therapy for the treatment of PD, although studies involving humans have been limited by their small samples and brief follow-up [31]. Further research including RCT in humans is need to prove that stem cell therapy is promising for the treatment of PD.

The pathways that are involved in the susceptibility of specific viscera to fibrosis or to systemic fibrosis

require additional delineation in order to gain a more comprehensive appreciation of the shared molecular changes that may underlie the fibrosis seen in PD; such an understanding would also offer further information relating to additional benign disorders of the urology system, e.g., ED. A requisite for the innovation of de novo treatments for either disease prevention or modification is a comprehensive understanding of the spectrum of signaling pathways responsible for fibrosis in PD. Therapies in the future may be most efficacious if interventions were directed toward a number of molecular targets within the fibrotic process owing to pathway redundancy.

Although we have described the useful options of the frequentist approach in addition to Bayesian analysis, the interpretation of the tendency obtained through the frequentist approach should be very cautious due to the number of studies and heterogeneity.

CONCLUSIONS

At present, there are no clinical treatment alternatives which, when contrasted against a placebo, have demonstrated effectiveness. These findings may reflect the restricted available information relating to the disease mechanisms underlying PD and the associated fibrotic conditions. Nevertheless, as the frequentist approach indicated that a number of pharmaceutical agents were efficacious, it is anticipated that more effective therapeutic options will be developed following further research.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: JHK. Data curation: SRS. Formal analysis: HYL. Methodology: SRS. Project administration: JHP. Resources: HYL. Visualization: JHP. Writing – original draft: HYL. Writing – review & editing: JHK.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.230016.

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