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Non-surgical therapies for Peyronie's disease (Review)

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[Intervention Review]

Non-surgical therapies for Peyronie's disease

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ABSTRACT

Background

Peyronie's disease is a condition that results in the development of penile plaques that can lead to penile curvature, pain, and erectile dysfunction, making sexual activity difficult. A number of non-surgical interventions exist to improve this condition, which include topical and injection agents as well as mechanical methods; however, their effectiveness remains uncertain. We performed this review to determine the effects of these non-surgical treatments.

Objectives

To assess the effects of non-surgical therapies compared to placebo or no treatment in individuals with Peyronie's disease.

Search methods

We performed a comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, Google Scholar, and Web of Science), trials registries, other sources of grey literature, and conference proceedings, up to 23 September 2022. We applied no restrictions on publication language or status.

Selection criteria

We included trials in which men with Peyronie's disease were randomized to undergo non-surgical therapies versus placebo or no treatment for penile curvature and sexual function.

Data collection and analysis

Two of four review authors, working in pairs, independently classified studies and abstracted data from the included studies. Primary outcomes were: patient-reported ability to have intercourse, quality of life, and treatment-related adverse effects. Secondary outcomes were: degree of penile curvature, discontinuation from treatment (for any reason), subjective patient-reported change in penile curvature, and improvement in penile pain. We performed statistical analyses using a random-effects model. We rated the certainty of evidence (CoE) according to the GRADE approach.

Main results

Our search identified 1288 relevant references of which we included 18 records corresponding to 14 unique randomized controlled trials (RCTs) with 1810 men. These informed 10 distinct comparisons with relevant outcome data that were mostly extracted from single trials. In this abstract, we focus only on the most clinically relevant comparisons for the three primary outcomes and also include the outcome of degree penile curvature.

Injectional collagenase (short-term): We found no short-term evidence on injectional collagenase for patients' self-reported ability to have intercourse and treatment-related adverse effects compared to placebo injection. Injectional collagenase may result in little to no difference in quality of life (scale 0 to 20 with lower scores indicating better quality of life; mean difference (MD) 1.8 lower, 95% confidence interval (CI) -3.58 to -0.02; 1 study, 134 participants; low CoE) and there may be little to no effect on the degree of penile curvature (MD 10.90 degrees less, 95% CI -16.24 to -5.56; 1 study, 136 participants; low CoE).

Injectional collagenase (long-term): We also found no long-term evidence on injectional collagenase for patients' self-reported ability to have intercourse compared to placebo injection. It likely results in little to no effect on quality of life (MD 1.00 lower, 95% CI -1.60 to -0.40; 1 study, 612 participants; moderate CoE). Treatment-related adverse effects are likely increased (risk ratio (RR) 2.32, 95% CI 1.98 to 2.72; 1 study, 832 participants; moderate CoE). Injectional collagenase likely results in little to no change in the degree of penile curvature (MD 6.90 degrees less, 95% CI -9.64 to -4.14; 1 study, 612 participants; moderate CoE).

Injectional verapamil (short-term): We are very uncertain how injectional verapamil may affect patients' self-reported ability to have intercourse compared to placebo injection short-term (RR 7.00, 95% CI 0.43 to 114.70; 1 study, 14 participants; very low CoE). We found no evidence for the outcome of quality of life. We are very uncertain how injectional verapamil may affect treatment-related adverse effects (RR not estimable; 1 study, 14 participants; very low CoE). Similarly, we are very uncertain how injectional verapamil may affect degree of penile curvature (MD -1.86, 95% CI -10.39 to 6.67; 1 study, 14 participants; very low CoE). We found no long-term data for any outcome.

Extracorporeal shock wave treatment (ESWT) (short-term): We are very uncertain how ESWT affects patients' self-reported ability to have intercourse short-term (RR 1.60, 95% CI 0.71 to 3.60; 1 study, 26 participants; very low CoE). ESWT may result in little to no difference in quality of life (MD 3.10, 95% CI 1.57 to 4.64; 2 studies, 130 participants; low CoE). We are very uncertain if ESWT has an effect on treatment-related adverse effects (RR 2.73, 95% CI 0.74 to 10.14; 3 studies, 166 participants; very low CoE). ESWT may result in little to no difference in the degree of penile curvature compared to placebo (RR -2.84, 95% -7.35 to 1.67; 3 studies, 166 participants; low CoE). We found no long-term data for any outcome.

Penile traction therapy (short-term): We found no evidence for whether penile traction compared to no treatment affects patients' self-reported ability to have intercourse. We are very uncertain how traction therapy may affect quality of life (MD 1.50 lower, 95% CI -3.42 to 0.42; 1 study, 90 participants; very low CoE). We are also very uncertain how traction therapy may affect treatment-related adverse effects (RR not estimable; 1 study, 90 participants; very low CoE) and how it affects the degree of curvature (MD 7.40 degrees less, 95% CI -11.18 to -3.62; 1 study, 89 participants; very low CoE). We found no long-term data for any outcome.

Authors' conclusions

There is little evidence supporting the effectiveness of most non-surgical treatments for Peyronie’s disease. Existing trials are mostly of poor methodological quality and/or fail to address patient-centered outcomes. Injectional collagenase appears to have some effectiveness; however, many individuals may not experience the improvement as clinically relevant, and this comes with the risk of increased adverse events. There is a critical need for better non-surgical treatment options for men with Peyronie’s disease.

PLAIN LANGUAGE SUMMARY

Non-surgical therapy for Peyronie's disease

Review question

In men with Peyronie's disease, how do treatments that are not surgery, such as pills, creams, injections, or treatments using shock waves, affect men's reported sexual function?

Background

Peyronie's disease may cause penile curvature, pain, or both, which makes it difficult to perform penetrative intercourse. Aside from surgery, many other treatments may or may not help with this disease, but it is unclear how well they work.

Methods

We used the recommended Cochrane methods, including GRADE to rate the certainty of the evidence.

Search date

The findings of our review are up-to-date to 23 September 2022.

Study characteristics

We included 14 trials in 1810 men with Peyronie's disease. We only included studies that compared these treatments to placebo (a similar-looking pill or injection with no active drug), sham (pretend) treatment, or no treatment. We only included studies in which chance decided what treatment the men got.

Key results

We found evidence for 10 different types of treatment that did not involve a surgical procedure. Here in this summary, we focus on the ones that experts told us were the most important to know about. Also, here we only report on the three main outcomes: patients' self-reported ability to have intercourse, their quality of life, and side effects. We also summarize data on the degree of penile curvature.

Injectional collagenase (short-term): We found no evidence about how injectional collagenase affects patients' self-reported ability to have intercourse or causes treatment-related unwanted side effects in the short term. Injectional collagenase may result in little to no difference in quality of life. There may be little to no effect on the degree of penile curvature.

Injectional collagenase (long-term): We also found no evidence about how injectional collagenase affects patients' self-reported ability to have intercourse in the long term. Injectional collagenase likely results in little to no difference in quality of life, but likely increases unwanted side effects. Also, in the long term, it may result in little to no change in the degree of penile curvature.

Injectional verapamil (short-term): We are very uncertain how injectional verapamil may affect patients' self-reported ability to have intercourse. We found no evidence for the outcome of quality of life. We are very uncertain how injectional verapamil may affect treatment-related side effects. Similarly, we are very uncertain how injectional verapamil may affect the degree of penile curvature.

We found no long-term data for any outcome.

Extracorporeal shock wave treatment (ESWT): We are very uncertain how ESWT affects patients' self-reported ability to have intercourse. ESWT may result in little to no difference in quality of life. We are again very uncertain if ESWT has an effect on treatment-related side effects. ESWT may result in little to no difference in the degree of penile curvature compared to placebo.

We found no long-term data for any outcome.

Penile traction therapy (short-term): We found no evidence about whether penile traction therapy compared to no treatment affects patients' self-reported ability to have intercourse. We are very uncertain how traction therapy may affect quality of life. We are also very uncertain how traction therapy may affect treatment-related side effects and how it affects the degree of curvature.

We found no long-term data for any outcome.

Certainty of the evidence

The certainty of the evidence is mainly very low or low for most of the interventions assessed. The certainty of the evidence is moderate for injectional collagenase (long-term outcomes). This means that our confidence in the results ranges from very low to moderate (and is mostly very low).

Summary of findings 1. Potassium paraaminobenzoate compared to placebo for Peyronie's disease (short-term)

Patient or population: men with acute (maximum of 12 months) Peyronie's disease with no prior treatment and no evidence of calcified plaques (pain during erection: 39 (37%) patients)
Setting: likely outpatient/multicenter (11 centers)/Germany
Intervention: oral potassium paraaminobenzoate
Comparison: oral placebo

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Interpretation
				Risk with placebo	Risk difference with potassium paraaminobenzoate	
Patient-reported ability to have intercourse Follow-up: 12 months MCID: 25% relative risk increase/decrease	75 (1 RCT)	⊕⊕⊖⊖ **LOW**[a,b]	**RR 1.19** (0.87 to 1.62)	**Study population**		There may be little to no difference in patient-reported ability to have intercourse between potassium paraaminobenzoate and placebo.
				625 per 1000	119 more per 1000 (81 fewer to 388 more)	
Quality of life	—	—	—	—		Not reported.
Treatment-related adverse effects Follow-up: 12 months MCID: 25% relative risk increase/decrease	103 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,c]	**RR 1.27** (0.36 to 4.48)	**Study population**		We are very uncertain how potassium paraaminobenzoate may affect treatment-related adverse effects.
				77 per 1000	21 more per 1000 (49 fewer to 268 more)	
Degree of penile curvature	—	—	—	—		Not reported.
Discontinuation from treatment Follow-up: 12 months MCID: 25% relative risk increase/decrease	103 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,c]	**RR 1.36** (0.72 to 2.58)	**Study population**		We are very uncertain how potassium paraaminobenzoate may affect discontinuation from treatment.
				231 per 1000	83 more per 1000 (65 fewer to 365 more)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level due to study limitations: unclear risk of selection bias, high risk of attrition bias, and unclear risk of reporting bias.
[b]Downgraded by one level for imprecision: CI crosses assumed MCID threshold.
[c]Downgraded by two levels for imprecision: very wide CI crosses assumed MCID threshold twice.

Summary of findings 2. Injectional interferon alpha-2B compared to saline for Peyronie's disease (short-term)

Patient or population: men with chronic (≥ 12 months) Peyronie's disease (single plaque)
Setting: likely outpatient/8 centers/USA
Intervention: interferon alpha-2B injection
Comparison: saline injection

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Interpretation
				Risk with saline	Risk difference with interferon alpha-2B	
Patient-reported ability to have intercourse	—	—	—	—	—	Not reported.
Quality of life	—	—	—	—	—	Not reported.
Treatment-related adverse effects	—	—	—	—	—	Not reported.
Degree of penile curvature Assessed with: protractor Follow-up: 4 weeks after end of treatment MCID: 12.5 degrees change from baseline[a]	103 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[b,c,d]	—	The mean degree of penile curvature was 46.4 degrees	**MD 10 degrees lower** (15.95 lower to 4.05 lower)	We are very uncertain how interferon alpha-2B may affect degree of penile curvature.
Discontinuation from treatment Follow-up: 4 weeks after end of treatment MCID: 25% relative risk increase/decrease	117 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[b,c,e]	**RR 0.63** (0.22 to 1.76)	**Study population**		We are very uncertain how interferon alpha-2B may affect discontinuation from treatment.
				145 per 1000	54 fewer per 1000	

						(113 fewer to 110 more)

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]MCID: 25% improvement (greater than 12.5 degrees) from the baseline.
[b]Downgraded by one level for study limitations: unclear or high risk of bias in almost all domains.
[c]Downgraded by one level for indirectness: only participants with single plaque were included.
[d]Downgraded by one level for imprecision: wide CI crosses assumed MCID threshold.
[e]Downgraded by two levels for imprecision: very wide CI crosses assumed MCID threshold twice.

Summary of findings 3. Injectional nicardipine compared to saline for Peyronie's disease (long-term)

Patient or population: men with chronic Peyronie's disease (plaques without calcification)
Setting: likely outpatient/Japan
Intervention: nicardipine injection
Comparison: saline injection

Outcomes (Follow-up)	**№** of participants (studies)	**Certainty of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects*** (95% CI)		**Interpretation**
				Risk with saline	**Risk difference with nicardipine**	
Patient-reported ability to have intercourse	—	—	—	—	—	Not reported.
Quality of life	—	—	—	—	—	Not reported.
Treatment-related adverse effects Follow-up: 38 weeks after end of treatment MCID: 25% relative risk increase/decrease	62 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**RR 2.82** (0.12 to 66.62)	**Study population**[c]		We are very uncertain how nicardipine may affect treatment-related adverse effects.
				—	—	

Degree of penile curvature Assessed with: photograph Follow-up: 38 weeks after end of treatment MCID: greater than 7.5 degree change from the baseline[d]	62 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	—	The mean degree of penile curvature was 29.1	**MD 3.3 lower** (7.62 lower to 1.02 higher)	We are very uncertain how nicardipine may affect degree of penile curvature.
Discontinuation from treatment Follow-up: 38 weeks after end of treatment MCID: 25% relative risk increase/decrease	74 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**RR 0.71** (0.25 to 2.05)	**Study population**		We are very uncertain how nicardipine may affect discontinuation from treatment.
				189 per 1000	55 fewer per 1000 (142 fewer to 199 more)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: unclear risk of selection bias, high risk of performance bias, and unclear risk of selective reporting bias.
[b]Downgraded by two levels for imprecision: very wide CI crosses assumed MCID with insufficient information size.
[c]No event in control group.
[d]MCID: 25% improvement (greater than 7.5 degree) from the baseline.

Summary of findings 4. Injectional betamethasone compared to saline for Peyronie's disease (long-term)

Patient or population: men with Peyronie's disease (not defined)
Setting: likely outpatient/single institute/Italy
Intervention: betamethasone injection
Comparison: saline injection

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Interpretation

				Risk with saline	Risk difference with betamethasone	
Patient-reported ability to have intercourse	—	—	—	—	—	Not reported.
Quality of life	—	—	—	—	—	Not reported.
Treatment-related adverse effects (long-term) Follow-up: 28 weeks after end of treatment MCID: 25% relative risk increase/decrease	30 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**Not estimable**	**Study population**[c] —	— —	We are very uncertain how betamethasone may affect treatment-related adverse effects.
Degree of penile curvature	—	—	—	—	—	Not reported.
Discontinuation from treatment Follow-up: 28 weeks after end of treatment **MCID:** 25% relative risk increase/decrease	30 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**Not estimable**	**Study population**[c] —	— —	We are very uncertain how betamethasone may affect discontinuation from treatment.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: unclear or high risk of bias in half or more domains.
[b]Downgraded by two levels for imprecision: presumed very wide CI would cross assumed MCID threshold twice.
[c]No events in either group.

Summary of findings 5. Injectional collagenase compared to placebo for Peyronie's disease (short-term)

Injectional collagenase compared to placebo for Peyronie's disease (short-term)

Patient or population: men with Peyronie's disease (diagnosis of disease: at least 12 months, penile curvature: at least 30 degrees)
Setting: likely outpatient/64 sites/USA and Australia

Intervention: collagenase injection
Comparison: placebo injection

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Interpretation
				Risk with placebo	Risk difference with injectional collagenase	
Patient-reported ability to have intercourse	—	—	—	—	—	Not reported.
Quality of life Assessed with: Peyronie's disease patient-reported outcome questionnaire: higher scores indicate worse quality of life Scale from: 0 to 20 Follow-up: 18 weeks after end of treatment MCID: greater than 2-point change from the baseline[c]	134 (1 RCT)	⊕⊕⊖⊖ **LOW**[a,b]	—	The mean change in quality of life was -0.75	**MD 1.80 lower** (3.58 lower to 0.02 lower)	There may be little to no difference in quality of life between collagenase and placebo.
Treatment-related adverse effects	—	—	—	—	—	Not reported.
Degree of penile curvature Assessed with: protractor Follow-up: 18 weeks after end of treatment MCID: greater than 12 degree change from the baseline[d]	136 (1 RCT)	⊕⊕⊖⊖ **LOW**[a,b]	—	The mean change in degree of penile curvature was -5.4 degrees	**MD 10.90 degrees lower** (16.24 lower to 5.56 lower)	There may be little to no difference in degree of penile curvature between collagenase and placebo.
Discontinuation from treatment	—	—	—	—	—	Not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: high risk of reporting bias.
[b]Downgraded by one level for imprecision: CI crosses assumed MCID threshold.
[c]MCID: 25% improvement (greater than 2 points) from the baseline (collagenase: 8.0/placebo: 8.1).
[d]MCID: 25% improvement (greater than 12 degrees) from the baseline.

Summary of findings 6. Injectional collagenase compared to placebo for Peyronie's disease (long-term)

Patient or population: men with Peyronie's disease (diagnosis of disease: at least 12 months, penile curvature: at least 30 degrees)
Setting: likely outpatient/64 sites/USA and Australia
Intervention: collagenase injection
Comparison: placebo injection

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Interpretation
				Risk with placebo	Risk difference with injectional collagenase	
Patient-reported ability to have intercourse	—	—	—	—	—	Not reported.
Quality of life Assessed with: PD questionnaire bother domain: higher scores indicate worse quality of life Scale from: 0 to 16 Follow-up: 28 weeks after end of treatment MCID: greater than 1.9 points change from the baseline[b]	612 (1 RCT)	⊕⊕⊕⊖ **MODERATE**[a]	—	The mean change in quality of life was -1.8	**MD 1.00 lower** (1.60 lower to 0.40 lower)	Collagenase likely results in little to no difference in quality of life compared to placebo.
Treatment-related adverse effects Follow-up: 28 weeks after end of treatment MCID: 25% relative risk increase/decrease	832 (1 RCT)	⊕⊕⊕⊖ **MODERATE**[a]	**RR 2.32** (1.98 to 2.72)	**Study population**		Collagenase likely results in an increase in treatment-related adverse effects when compared to placebo.
				363 per 1000	479 more per 1000 (356 more to 624 more)	

Degree of penile curvature Assessed with: goniometer Follow-up: 28 weeks after end of treatment MCID: greater than 12 degree change from the baseline[c]	612 (1 RCT)	⊕⊕⊕⊖ **MODERATE**[a]	—	The mean change in degree of penile curvature was -9.3 degrees	**MD 6.90 degrees lower** (9.64 lower to 4.16 lower)	Collagenase likely results in little to no difference in degree of penile curvature compared to placebo.
Discontinuation from treatment Follow-up: 28 weeks after end of treatment MCID: 25% relative risk increase/decrease	836 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,d]	**RR 1.25** (0.84 to 1.86)	**Study population**		We are very uncertain how collagenase may affect discontinuation from treatment when compared to placebo.
				107 per 1000	27 more per 1000 (17 fewer to 92 more)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: unclear or high risk of selection and/or attrition bias.
[b]Minimal clinically important difference: 25% improvement (greater than 1.9 points) from the baseline (collagenase: 7.5/placebo: 7.8).
[c]Minimal clinically important difference: 25% improvement (greater than 12 degrees) from the baseline (collagenase: 50/placebo: 49).
[d]Downgraded by two levels for imprecision: very wide confidence interval crosses assumed minimal clinically important difference threshold twice.

Summary of findings 7. Injectional verapamil versus saline (short-term)

Patient or population: men with Peyronie's disease (palpable plaque or pain)
Setting: likely outpatient/single-center/USA
Intervention: verapamil injection
Comparison: placebo injection

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	Interpretation

				Risk with placebo	Risk difference with injectional collagenase	
Patient-reported ability to have intercourse Follow-up: 3 months after end of treatment MCID: 25% relative risk increase/decrease	14 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**RR 7.00** (0.43 to 114.70)	**Study population**[c] —	— —	We are very uncertain how verapamil may affect patient-reported ability to have intercourse.
Quality of life	—	—	—	—	—	Not reported.
Treatment-related adverse effects Follow-up: 3 months after end of treatment MCID: 25% relative risk increase/decrease	14 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,d]	**Not estimable**	**Study population**[c] —	— —	We are very uncertain how verapamil may affect treatment-related adverse effects.
Degree of penile curvature assessed with: protractor Follow-up: 3 months after end of treatment MCID: 25% relative risk increase/decrease[e]	14 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	—	The mean degree of penile curvature was 31.43 degrees	**MD 1.86** degrees lower (10.39 lower to 6.67 higher)	We are very uncertain how verapamil may affect penile curvature.
Discontinuation from treatment	—	—	—	**Study population** —	— —	Not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: unclear or high risk of bias in half or more domains.
[b]Downgraded by two levels for imprecision: very wide CI crosses assumed MCID threshold twice.
[c]No event in either group.
[d]Downgraded by two levels for imprecision: no events; presumed very wide CI would cross assumed MCID threshold twice.
[e]MCID: 8 degrees, which corresponds to 25% improvement from the baseline (verapamil: 37.1/saline: 33.6).

Summary of findings 8. Injectional Botox compared to placebo for Peyronie's disease (short-term)

Patient or population: men with Peyronie's disease (stable phase)
Setting: likely outpatient/single institute/Italy
Intervention: injectional Botox injection
Comparison: injectional saline injection

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Interpretation
				Risk with placebo	Risk difference with injectional Botox	
Patient-reported ability to have intercourse	—	—	—	—	—	Not reported.
Quality of life Assessed with: International Index of Erectile Function questionnaire: higher scores indicate better quality of life Scale from: 0 to 5 Follow-up: 16 weeks MCID: greater than 1.2 point change from the baseline[a]	12 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[b,c]	—	The mean quality of life was -0.67	**MD 0.67 higher** (1.5 lower to 2.84 higher)	We are very uncertain how Botox may affect quality of life.
Treatment-related adverse effects	—	—	—	—	—	Not reported.
Degree of penile curvature	—	—	—	—	—	Not reported.
Discontinuation from treatment	—	—	—	—	—	Not reported.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]MCID: 25% improvement (greater than 1.2 points) from the baseline (Botox: 4.8/placebo: 5.8).
[b]Downgraded by one level for study limitations: unclear risk of bias in most domains
[c]Downgraded by two levels for imprecision: very wide CI crosses assumed MCID threshold twice.

Summary of findings 9. Extracorporeal shock wave treatment (ESWT) compared to sham for Peyronie's disease (short-term)

Patient or population: men with Peyronie's disease (penile plaque with pain and/or curvature, diagnosis of disease: from acute (< 12 months) to chronic (> 12 months))
Setting: likely outpatient/single institute/Europe
Intervention: ESWT
Comparison: sham

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)		Interpretation
				Risk with sham	Risk difference with ESWT	
Patient-reported ability to have intercourse Follow-up: range 10 weeks to 26 weeks after end of treatment MCID: 25% relative risk increase/decrease	26 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**RR 1.60** (0.71 to 3.60)	**Study population**		We are very uncertain how ESWT may affect patient-reported ability to have intercourse.
				385 per 1000	231 more per 1000 (112 fewer to 1000 more)	
Quality of life Assessed with IIEF-5: higher scores indicate a better outcome Scale from: 0 to 25 Follow-up: range 12 weeks to 24 weeks after end of treatment MCID: greater than 4-point change from the baseline[c]	130 (2 RCTs)	⊕⊕⊖⊖ **LOW**[a,d]	—	The mean quality of life ranged from 18.75 to 19.62	**MD 3.10 higher** (1.57 higher to 4.64 higher)	ESWT may result in little to no difference in quality of life compared to no treatment
Treatment-related adverse effects Follow-up: range 4 weeks to 26 weeks after end of treatment MCID: 25% relative risk increase/decrease	166 (3 RCTs)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**RR 2.73** (0.74 to 10.14)	**Study population**		We are very uncertain how ESWT may affect treatment-related adverse effects.
				29 per 1000	49 more per 1000 (7 fewer to 261 more)	

Degree of penile curvature Assessed with: goniometer Follow-up: range 4 weeks to 26 weeks after end of treatment MCID: greater than 7 degree change from the baseline[e]	166 (3 RCTs)	⊕⊕⊖⊖ **LOW**[a,d]	—	The mean degree of penile curvature ranged from 28 to 31 degrees	**MD 2.84 degrees lower** (7.35 lower to 1.67 higher)	ESWT may result in little to no difference in degree of penile curvature compared to placebo.
Discontinuation from treatment Follow-up: range 4 weeks to 26 weeks after end of treatment MCID: 25% relative risk increase/decrease	238 (4 RCTs)	⊕⊖⊖⊖ **VERY LOW**[a,b]	**RR 0.57** (0.06 to 5.65)	**Study population**		We are very uncertain how ESWT may affect discontinuation from treatment.
				15 per 1000	6 fewer per 1000 (14 fewer to 68 more)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **IIEF:** International Index of Erectile Function; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by one level for study limitations: unclear risk of bias for selection bias and selective reporting bias.
[b]Downgraded by two levels for imprecision: very wide CI crosses assumed minimal clinically important difference threshold twice.
[c]MCID: 25% improvement (greater than 4 points) from the baseline (ESWT: 16/sham: 17).
[d]Downgraded by one level for imprecision: CI crosses assumed MCID threshold.
[e]MCID: 25% improvement (greater than 7 degrees) from the baseline (ESWT: 27/sham: 30).

Summary of findings 10. Penile traction therapy versus no treatment (short-term)

Patient or population: men with Peyronie's disease (diagnosis of disease: varying, penile curvature: at least 30 degrees)
Setting: 6 centers: Spain, India, Germany, USA
Intervention: penile traction therapy
Comparison: no traction therapy

Outcomes (Follow-up)	№ of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	Interpretation

				Risk with no treatment	Risk difference with penile traction therapy	
Patient-reported ability to have intercourse	—	—	—	—	—	Not reported.
Quality of life Assessed with: PD questionnaire symptom bother domain: high score indicate worse quality of life Follow-up: 3 months after end of treatment MCID: greater than 2.2 point change from the baseline[a]	82 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[b,c]	—	The mean quality of life was -0.9	**MD 1.50 lower** (3.42 lower to 0.42 higher)	We are very uncertain how penile traction therapy affects quality of life.
Treatment-related adverse effects Follow-up: 3 months after end of treatment MCID: 25% relative risk increase/decrease	90 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[b,c]	**Not estimable**	**Study population**		We are very uncertain how penile traction therapy affects treatment-related adverse effects.
				—	—	
Degree of penile curvature Assessed with: protractor Follow-up: 3 months after end of treatment MCID: greater than 11 degree change from the baseline[e]	89 (1 RCT)	⊕⊖⊖⊖ **VERY LOW**[b,c]	—	The mean degree of penile curvature was 1.1 degree lower	**MD 7.40 degrees lower** (11.18 lower to 3.62 lower)	We are very uncertain how penile traction therapy affects degree of penile curvature.
Discontinuation from treatment Follow-up: 3 months after end of treatment MCID: 25% relative risk increase/decrease	182 (2 RCTs)	⊕⊖⊖⊖ **VERY LOW**[b,c]	**RR 0.86** (0.31 to 2.36)	**Study population**		We are very uncertain how penile traction therapy affects discontinuation from treatment.
				96 per 1000	13 fewer per 1000 (66 fewer to 130 more)	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MCID**: minimal clinically important difference; **MD:** mean difference; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]MCID: 25% improvement (greater than 2.2 points) from the baseline (penile traction: 8.7/control: 9.8).
[b]Downgraded by one level due to study limitations: unclear or high risk of bias in several domains.
[c]Downgraded by two levels for imprecision: very wide CI crosses assumed MCID twice or very rare event with insufficient information size.
[d]No event in either group.
[e]MCID: 25% improvement (greater than 11 degrees) from the baseline (penile traction: 45.4/control: 44.2).

BACKGROUND

Description of the condition

Peyronie's disease is defined in the American Urological Association's 2015 guideline as an "acquired penile abnormality characterized by fibrosis of the tunica albuginea, which may be accompanied by pain, deformity, erectile dysfunction, and/or distress" (Nehra 2015). It is more commonly known as a disorder of penile curvature and/or plaque caused by fibrosis or scar tissue that interfere with the ability to have intercourse. It is hypothesized that Peyronie's disease begins with buckling trauma of the tunica albuginea resulting in intravasation of blood and immune-mediated cells and, with it, activation of fibrinogen. Cytokines, fibrin, neutrophils, platelets, and autacoids are entrapped, which may develop into fibrosis (Mulhall 2003; Somers 1989). Based on studies, the range of the disease's prevalence is best estimated to be between 1% and 20% of adult men depending on age, nationality, and comorbidities, with the average age of onset being 53 years (Arafa 2007; DiBenedetti 2011). Clinically, it manifests with varying severity and direction of curvature, erectile dysfunction (ED), penile shortening, and pain. Almost half of patients with Peyronie's disease suffer from depression and relationship stress, while 81% are emotionally distressed due to the physical nature and self-image of the penile deformity (Randhawa 2019). It is accepted that there are two phases of the disease: an acute active phase, which may be associated with painful erections, and evolving deformity resolving by 12 to 18 months, followed by a secondary phase of dormancy in which the fibrosis stabilizes (Hatzimouratidis 2012). Non-surgical intervention is likely most effective during the active phase of the disease when inflammation is treatable (Pryor 2002).

Description of the intervention

Non-surgical interventions for Peyronie's disease can be broadly categorized into oral, topical, injectional, or mechanical therapy. These include colchicine, potassium paraaminobenzoate, verapamil, tamoxifen, iontophoresis, interferon alpha-2 beta, shock wave therapy, collagenase, and mechanical traction. Each of these have different mechanisms of action.

Adverse effects of the intervention

In general, adverse effects may include erectile dysfunction, pain with erections, worsening penile curvature, hematoma requiring intervention, and systemic side effects of oral medications.

How the intervention might work

Various non-surgical interventions have been attempted to improve penile curvature, including oral, topical, injectional, and mechanical methods (Chung 2020; Chung 2022). Each may involve daily or weekly treatments depending on the intervention.

Potassium paraaminobenzoate (POTABA)

Potassium paraaminobenzoate has anti-fibrotic and anti-inflammatory effects, with stabilization of the tissue serotonin-monoamine oxidase activity and a direct inhibitory effect on fibroblast glycosaminoglycan secretion. It has previously been used to treat other fibrotic altering diseases such as dermatomyositis and scleroderma (Park 2016).

Interferon alpha-2 beta

Interferons alter the metabolic activity of myofibroblasts in vitro and decrease fibroblast and collagen proliferation with an increase in collagenase production (Hellstrom 2006; Inal 2006).

Nicardipine injection

Calcium channel antagonists decrease fibroblast-related secretion of collagen (Chong 2016).

Betamethasone injection

Betamethasone is corticosteroid, which has anti-inflammatory and subsequently anti-fibrotic effects. Injectional use has been previously attempted for other fibrotic diseases such as oral submucous fibrosis (Goel 2015).

Collagenase *Clostridium histolyticum* injection

A purified form of AUX-1 and AUX-2 collagenases that target specifically collagen types I and III, which is meant to enzymatically disrupt the formed plaque, induce apoptosis of fibroblasts, and decrease expression of TGF-B and fibronectin (Gelbard 2013; Palmieri 2009).

Verapamil injection

Verapamil is a calcium channel blocker; it remodels and degrades extracellular fibrosis. It has been shown to inhibit the synthesis/secretion of extracellular matrix molecules including collagen, glycosaminoglycans, and fibronectin. It also increases collagenase, modifies transforming growth factor beta (TGF-ß) activity, and has improved penile pressures (Rehman 1998).

Botulinum toxin injection

Botulinum toxin is thought to reduce scar formation. The exact mechanism is unknown, but Lee 2009 hypothesized that botulinum toxin-induced paralysis of the musculature adjacent to the scar minimizes the repetitive tensile forces on the wound/scar edges, and this results in a decreased fibroblastic response and fibrosis of the wound.

Extracorporeal shock wave therapy (ESWT)

Used to break up calcifications that are the cause of plaque formation with mechanical shock wave energy.

Traction therapy

The application of continuous traction increases the activity of degradative enzymes. In vitro studies have shown that penile traction therapy decreases smooth muscle actin and increases matrix metalloproteinase activity within the treated tissue. Ultimately, mechano-transduction (a cellular process that translates mechanical stimuli into a chemical response that leads to activation of cell proliferation) via tissue traction leads to collagen degradation and scar remodeling, as evidenced by the re-orientation of collagen fibrils in line with the direction of applied force (Moncada 2019).

Why it is important to do this review

This Cochrane systematic review of the existing literature allows for an assessment of the most clinically relevant non-surgical treatment modalities for Peyronie's disease focused on clinically important outcomes. Currently, no such review exists that uses

the GRADE approach to rate the certainty of the evidence (Guyatt 2008). This review aims to inform treatment decisions and direct further research in this area. Given the lack of any established form of therapy of proven effectiveness, the focus was on comparisons with placebo/no treatment rather than a comparison of active interventions. We expect this review to have important implications for clinical decision-making at the point of care, help inform guideline recommendations, and support health policy and coverage decisions that should all be based on rigorous assessments of the current best evidence.

OBJECTIVES

To assess the effects of non-surgical therapies compared to placebo or no treatment in individuals with Peyronie's disease.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized or quasi-randomized trials. We included studies regardless of their publication status or language of publication. We did not consider cross-over trials or cluster-randomized controlled trials as they were not applicable to the comparisons of interest.

Types of participants

We included adult men over 18 years of age with a clinical diagnosis of Peyronie's disease, defined as symptomatic or bothersome acquired penile curvature.

If we identified studies in which only a subset of participants were relevant to this review, we included such studies if data were available separately for the relevant subset.

Types of interventions

We investigated the following comparisons of experimental intervention versus comparator intervention.

Experimental interventions

We investigated any non-surgical therapies for treatment of Peyronie's disease meeting our inclusion criteria. These included treatments were broadly categorized into three distinct categories:

- Oral therapies
- Injection therapies
- Mechanical therapies

Based on reviewers' feedback we excluded all topical agents as discussed in Differences between protocol and review.

Comparator interventions

- Placebo
- No treatment

Comparisons

We compared all interventions to placebo or no treatment, if data were available. Concomitant interventions had to be the same in the experimental and comparator groups to establish a fair comparison.

Types of outcome measures

We did not use the measurement of the outcomes assessed in this review as an eligibility criterion.

Primary outcomes

- Patient-reported ability to have intercourse
- Quality of life
- Treatment-related adverse effects

Secondary outcomes

- Degree of penile curvature
- Discontinuation from treatment
- Subjective patient-reported change in penile curvature
- Improvement in penile pain

Method and timing of outcome measurement

- Patient-reported ability to have intercourse
  - Number of participants achieving self-reported potency defined as an erection firm enough and of sufficient duration to have sexual intercourse.
- Quality of life
  - Final value or change assessed with validated questionnaires such as Peyronie's Disease Questionnaire (Hellstrom 2013) or International Index of Erectile Function (IIEF) (Rosen 1997).
- Treatment-related adverse effects
  - Number of participants experiencing adverse events such as erectile dysfunction, pain, hematoma requiring intervention (dichotomous variable for each encountered), and corporal rupture after treatment.
- Degree of penile curvature
  - Final value or change assessed with protractor or ultrasonography during full erection.
- Discontinuation from treatment
  - Treatment discontinuation from any cause at any time after participants were randomized to intervention/comparator groups.
- Subjective patient-reported change in penile curvature
  - Number of participants achieving self-reported improvement in penile curvature.
- Improvement in penile pain
  - Final value or change assessed with validated questionnaires such as a visual analog scale (VAS) or international pain score associated with curvature or plaque (DeLoach 1998).

We considered clinically important difference for the review outcomes to rate the certainty of the evidence for imprecision in the summary of findings tables (Jaeschke 1989; Johnston 2013). We used the minimal clinically important difference (MCID) of four-point change on the International Index of Erectile Function (IIEF-5). We considered the MCID for penile pain to be one point on a 10-point VAS for pain (Kelly 2001). There is no reported threshold for the outcomes of patient-reported ability to have intercourse, treatment-related adverse effects, discontinuation from treatment, and subjective patient-reported change in penile curvature. We therefore considered the clinically important difference for patient-reported ability to have intercourse, treatment-related adverse effects, discontinuation from treatment, and subjective patient-reported change in penile curvature for acceptability of the intervention to be a relative risk reduction or increase of at

least 25% (Guyatt 2011a). We used a minimal clinically important difference (MCID) of 25% improvement from baseline in quality of life and degree of penile curvature (Nickel 2015). There was a study reporting a threshold for degree of penile curvature based on patient implications (Ziegelmann 2017).

When encountering comparisons with no events in either group, we assumed a risk ratio of 1 to be the best approximation of the effect size. We interpreted the GRADE domain of imprecision by imputing a single event in each group, thereby allowing us to assess the width of the confidence interval in relationship to the assumed MCID.

We planned to assess the outcomes as short term and long term.

- Short term: up to six months after treatment
- Long term: more than six months after treatment

Main outcomes for summary of findings table

We present a summary of findings table reporting the following outcomes listed according to priority.

1. Patient-reported ability to have intercourse
2. Quality of life
3. Treatment-related adverse effects
4. Degree of penile curvature
5. Discontinuation from treatment

Search methods for identification of studies

We performed a comprehensive search with no restrictions on the language of publication or publication status. The date of the most recent search was 23 September 2022.

Electronic searches

We searched the following sources from the inception of each database. Our search strategy is detailed in Appendix 1.

- *Cochrane Library*
  - *Cochrane Database of Systematic Reviews* (CDSR)
  - Cochrane Central Register of Controlled Trials (CENTRAL)
  - Database of Abstracts of Reviews of Effects (DARE)
  - Health Technology Assessment Database (HTA)
- MEDLINE (PubMed)
- EMBASE via Ovid
- MetaRegister of Controlled Trials
- Australian Clinical Trials Registry
- Latin American and Caribbean Health Science Information Database (LILACS)

We also searched the following resources:

- ClinicalTrials.gov (www.clinicaltrials.gov/);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch/), a meta-register of studies with links to the numerous other trials registers;
- Annual meetings proceedings (2020-2022) for the:
  - Sexual Medicine Society of North America, Inc (SMSNA);
  - International Society for Sexual Medicine (ISSM);
  - European Society for Sexual Medicine (ESSM).

We have included the complete search strategy for MEDLINE (PubMed) in Appendix 1. We modified the electronic search strategies to incorporate any additional relevant keywords during any of the electronic or other searches.

Searching other resources

We identified other potentially eligible trials or ancillary publications by searching the reference lists of retrieved included trials, reviews, meta-analyses, and health technology assessment reports. We also contacted study authors of included trials to identify any further studies that we may have missed. We contacted drug/device manufacturers for ongoing or unpublished trials. We did not search abstract proceedings of relevant meetings such as the American Urological Association, European Association of Urology, International Society of Andrology, American Society of Andrology, and Society of Sexual Medicine (as planned for the last five years; 2017 to 2022) since these are now included in the electronic databases we searched.

Data collection and analysis

Selection of studies

We used EndNote (EndNote X7.4) as well as Covidence (Covidence) to identify and remove potential duplicate records. Two of four review authors (ECH, JHJ, JER, OE) independently scanned the abstract, title, or both, of the remaining records retrieved, to determine which records should be assessed further. Two of four review authors (ECH, JHJ, JER, OE) investigated all potentially relevant records as full text, mapped records to studies, and classified studies as included studies, excluded studies, studies awaiting classification, or ongoing studies, in accordance with the criteria for each provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We resolved any discrepancies through consensus or recourse to a third review author (MCR). If resolution of a disagreement was not possible, we designated the study as 'awaiting classification' and we contacted the study authors for clarification. We documented reasons for exclusion of studies that may have reasonably been expected to be included in the review in a Characteristics of excluded studies table. We presented an adapted Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram showing the process of study selection (Liberati 2009).

Data extraction and management

We developed a dedicated data abstraction form that we pilot tested ahead of time.

For studies that fulfilled the inclusion criteria, two of four review authors working in pairs (ECH, JHJ, JER, OE) independently abstracted the following information (see Characteristics of included studies):

- Study design.
- Study dates (if dates were not available then this was reported as such).
- Study settings and country.
- Participant inclusion and exclusion criteria.
- Participant details, baseline demographics such as age, degree of curvature, degree of erectile dysfunction, presence of pain, duration of symptoms.
- The number of participants by study and by study arm.

- Details of relevant experimental and comparator interventions such as dose, route, frequency, and duration.
- Definitions of relevant outcomes, and method and timing of outcome measurement as well as any relevant subgroups.
- Study funding sources.
- Declarations of interest by primary investigators.

We extracted relevant outcome data to this review as needed for calculation of summary statistics and measures of variance. For dichotomous outcomes, we attempted to obtain numbers of events and totals for population of a 2 x 2 table, as well as summary statistics with corresponding measures of variance. For continuous outcomes we attempted to obtain means and standard deviations or data necessary to calculate this information.

We resolved any disagreements by discussion or, if required, by consultation with a third review author (MCR).

We provided information, including trial identifier, about potentially relevant ongoing studies (see Characteristics of ongoing studies).

We attempted to contact authors of included studies to obtain key missing data as needed.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximized the yield of information by mapping all publications to unique studies and collating all available data, and we used the most complete data-set aggregated across all known publications. In case of doubt, we gave priority to the publication reporting the longest follow-up associated with our primary or secondary outcomes.

Assessment of risk of bias in included studies

Two of four review authors working in pairs (ECH, JHJ, JER, OE) assessed the risk of bias of each included study independently. We resolved disagreements by consensus, or by consultation with a third review author (MCR).

We assessed risk of bias using the Cochrane tool for risk of bias assessment (Higgins 2011b). We assessed the following domains.

- Random sequence generation (selection bias).
- Allocation concealment (selection bias).
- Blinding of participants and personnel (performance bias).
- Blinding of outcome assessment (detection bias).
- Incomplete outcome data (attrition bias).
- Selective reporting (reporting bias).
- Other sources of bias.

We judged risk of bias domains as 'low risk', 'high risk', or 'unclear risk' and evaluated individual bias items as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We present a risk of bias summary figure to illustrate these findings.

For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we evaluated the risk of bias separately for each outcome, and grouped outcomes according to whether they were measured subjectively or objectively when reporting our findings in the risk of bias tables.

We assessed attrition bias (incomplete outcome data) on an outcome-specific basis, and grouped outcomes with like judgments when reporting our findings in the risk of bias tables.

We further summarized the risk of bias across domains for each outcome in each included study, as well as across studies and domains for each outcome.

We defined the following endpoints as subjective outcomes.

- Patient-reported improvement in ability to have intercourse
- Quality of life
- Treatment-related adverse effects
- Degree of penile curvature
- Subjective patient-reported change in penile curvature
- Improvement in penile pain (associated with curvature or plaque)

We defined the following endpoint as an objective outcome.

- Discontinuation from treatment

Measures of treatment effect

We expressed dichotomous data as risk ratios (RRs) with 95% confidence intervals (CIs). We expressed continuous data as mean differences (MDs) with 95% CIs unless different studies use different measures to assess the same outcome, in which case we expressed data as standardized mean differences (SMDs) with 95% CIs.

Unit of analysis issues

The unit of analysis was the individual participant.

Dealing with missing data

We attempted to obtain missing data from study authors. When feasible, we performed intention-to-treat (ITT) analyses if data were available. We investigated attrition rates, e.g. dropouts, losses to follow-up, and withdrawals, and critically appraised issues of missing data. We did not impute missing data.

Assessment of heterogeneity

In the event of excessive heterogeneity unexplained by subgroup analyses, we did not report outcome results as the pooled effect estimate in a meta-analysis but provided a narrative description of the results of each study.

We identified heterogeneity (inconsistency) through visual inspection of the forest plots to assess the amount of overlap of CIs, and the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis (Higgins 2002; Higgins 2003). We interpreted I^2 as follows.

- 0% to 40%: may not be important.
- 30% to 60%: may indicate moderate heterogeneity.
- 50% to 90%: may indicate substantial heterogeneity.
- 75% to 100%: considerable heterogeneity.

When we found heterogeneity, we attempted to determine possible reasons for it by examining individual study and subgroup characteristics.

Assessment of reporting biases

We attempted to obtain study protocols to assess for selective outcome reporting.

We did not use funnel plots to assess for publication bias since all analyses included fewer than 10 studies.

Data synthesis

We summarized data using a random-effects model in accordance with Cochrane Urology editorial policy as providing the more conservative effect size estimates in most cases. In addition, we performed statistical analyses according to the statistical guidelines contained in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). For dichotomous outcomes, we used the Mantel-Haenszel method; for continuous outcomes, we used the inverse variance method. We used Review Manager 5 software to perform analyses (RevMan 2014).

Subgroup analysis and investigation of heterogeneity

We expected the following characteristics to introduce clinical heterogeneity, and planned to perform subgroup analyses with investigation of interactions.

1) Initial degree of curvature:

- Zero to 60 degrees
- Greater than 60 but less than 90 degrees
- Greater than 90 degrees

2) The timing of treatment to phase of the disease:

- Acute phase (pain with erections or changing degree of curvature)
- Stable phase (pain no longer present and curvature stable for greater than six months)

We were unable to perform any of these planned subgroup analyses.

Sensitivity analysis

We planned to perform sensitivity analyses for studies at low risk of bias, but were unable to do so.

Summary of findings and assessment of the certainty of the evidence

We presented the overall quality of the evidence for each outcome according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, which takes into account five criteria not only related to internal validity (risk of bias, inconsistency, imprecision, publication bias) but also to external validity such as directness of results (Guyatt 2008). For each comparison, two of four review authors working in pairs (ECH, JHJ, JER, OE) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low' using GRADEpro GDT; discrepancies were resolved by consensus or, if needed, by arbitration by a third review author (MCR). For each comparison, we presented a summary of the evidence for the main outcomes in a summary of findings table, which provides key information about the best estimate of the magnitude of the effect, in relative terms and absolute differences for each relevant comparison of alternative management strategies; numbers of participants and studies addressing each important outcome; and the rating of the overall confidence in effect estimates for each outcome (Guyatt 2011b; Schünemann 2011).

RESULTS

Description of studies

We completed a comprehensive literature search that yielded 1288 records. We found no applicable records in trial registers or the grey literature repository.

Results of the search

Our search of multiple databases yielded 1288 references. After exclusion of duplicates, we screened 1210 references at the title/abstract stage. Of these, 71 records entered the full-text screening stage; we excluded 53 records mapping to 46 studies. We ultimately included 18 records mapping to 14 unique studies in the quantitative analysis with 10 unique interventions. We presented details of included studies in the Characteristics of included studies. We summarized reasons for exclusion at the full-text stage in the PRISMA flow diagram (Figure 1), and we provided further detail in the Characteristics of excluded studies.

Figure 1. Flow diagram.

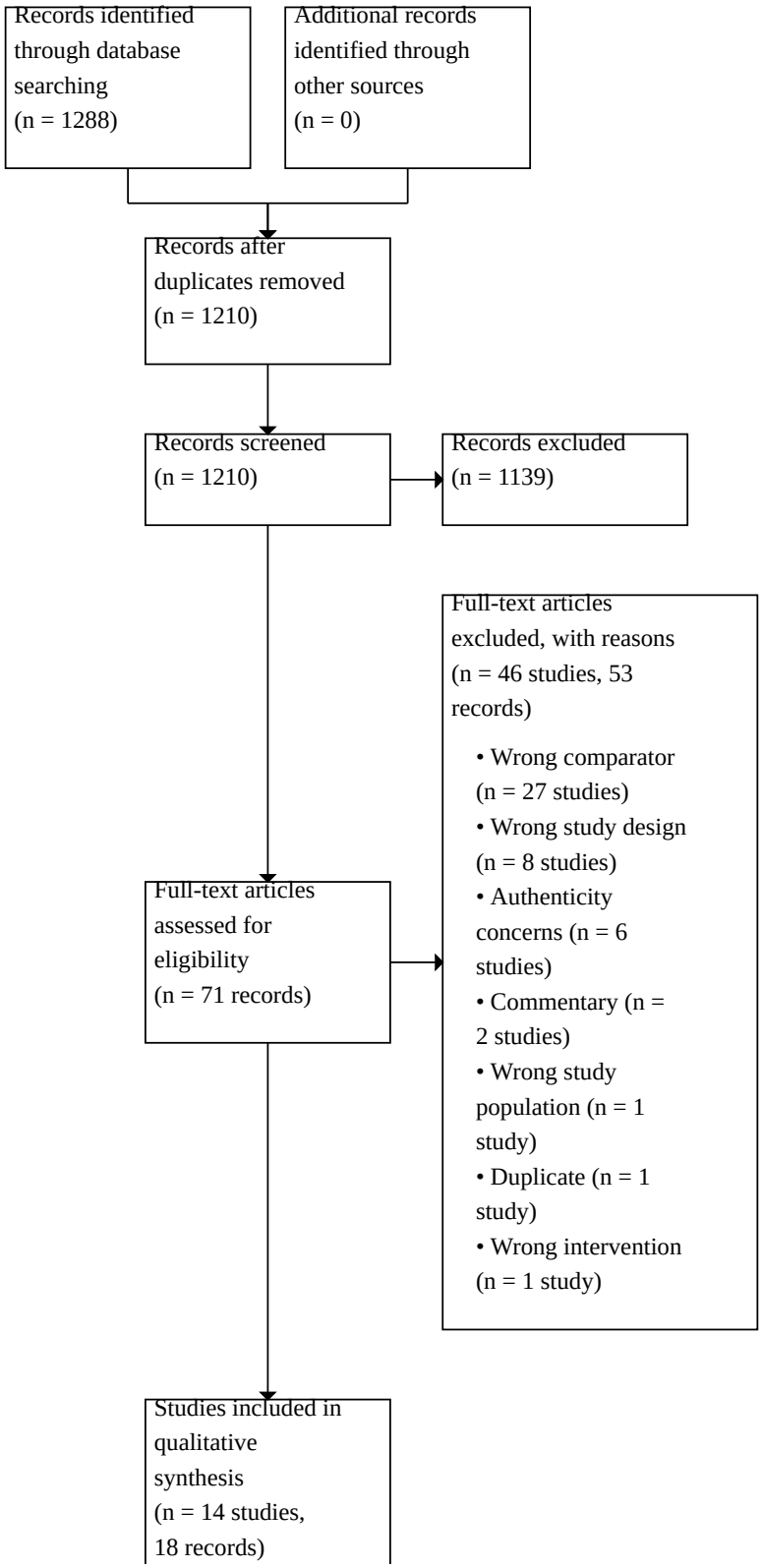
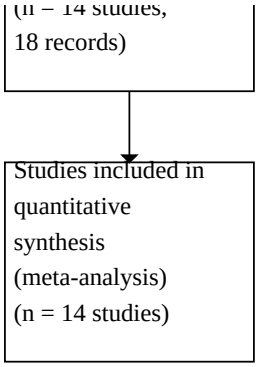


Figure 1. (Continued)



Included studies

We included 13 published studies in full text and one abstract proceeding (Antar 2019). All studies were published in English. We describe the included studies below; additional information is provided in Table 1 and Table 2.

Study design and settings

All studies were parallel randomized controlled trials (RCTs). Most were single-center trials (10/14); only four were multi-center trials (Gelbard 2012; Gelbard 2013; Hellstrom 2006; Weidner 2005). Accrual periods ranged from 1987 to 2020. Four trials did not report any information on their enrollment period. All but four comparisons (injectional betamethasone, collagenase, nicardipine, potassium paraaminobenzoate) had only short-term (up to six months) data available.

Participants

We included 1810 randomized participants, of whom 1636 completed the trials. Mean curvature ranged from 24.9 to 72.3 degrees. One trial included participants explicitly in the active phase of disease (Palmieri 2009). Six trials described including participants explicitly in the stable phase (Antar 2019; Chitale 2010; Gelbard 2013; Hatzichristodoulou 2013; Moncada 2019; Mortensen 2021). One trial included participants with a duration of disease less than 12 months (Weidner 2005), two trials included participants with duration of disease of at least six months (Gelbard 2012; Mortensen 2021), while two trials only included participants with presence of disease for more than 12 months (Hellstrom 2006; Rehman 1998). One trial included participants diagnosed with Peyronie's disease within 10 years with only 3% diagnosed within the past three months (Ziegelmann 2019). One trial included only participants in the transition between active and stable phase (Soh 2010), while the remaining trials did not report how long the participants have had Peyronie's disease. Eight trials stated they excluded participants who had received prior treatment for Peyronie's disease (Gelbard 2012; Gelbard 2013; Hatzichristodoulou 2013; Moncada 2019; Mortensen 2021; Palmieri 2009; Rehman 1998; Weidner 2005). This information is summarized in Table 1.

Interventions, comparators, and comparisons

In the 14 trials included, there were 11 unique interventions. These informed nine distinct comparisons with relevant outcomes (Table 2) of oral agents (n = 1), injectional agents (n = 6), and device-based applications (n = 2). Both short- and long-term outcomes were only available for collagenase injection.

The one oral agent for which we found an eligible study was on oral potassium paraaminobenzoate.

The six injectional agents for which we found eligible studies were on interferon alpha-2B, nicardipine, betamethasone, collagenase *Clostridium histolyticum,* verapamil, and botulinum toxin (Botox is the trade name).

The two mechanical therapies for which we found eligible studies were on extracorporeal shock wave treatment (ESWT) and penile traction.

We found evidence on therapies including colchicine, vitamin E and propionyl-L-carnitine (separately or in combination), omega-3 coenzyme Q10, pentoxifylline, and injectional verapamil, but excluded these studies due to concerns over data integrity.

Outcomes

Three studies reported on patient-reported ability to have intercourse (Hatzichristodoulou 2013; Rehman 1998; Weidner 2005), six reported on quality of life (Antar 2019; Gelbard 2012; Gelbard 2013; Mortensen 2021; Palmieri 2009; Ziegelmann 2019), nine on treatment-related adverse effects (Chitale 2010; Cipollone 1998; Gelbard 2013; Mortensen 2021; Palmieri 2009; Rehman 1998; Soh 2010; Weidner 2005; Ziegelmann 2019), nine on degree of penile curvature (Chitale 2010; Gelbard 2012; Gelbard 2013; Hellstrom 2006; Mortensen 2021; Palmieri 2009; Rehman 1998; Soh 2010; Ziegelmann 2019), 11 on discontinuation from treatment (Chitale 2010; Cipollone 1998; Gelbard 2013; Hatzichristodoulou 2013; Hellstrom 2006; Moncada 2019; Mortensen 2021; Palmieri 2009; Soh 2010; Weidner 2005; Ziegelmann 2019), six on subjective improvement in degrees of penile curvature (Cipollone 1998; Gelbard 2013; Hatzichristodoulou 2013; Mortensen 2021; Rehman 1998; Weidner 2005), and six on penile pain (Chitale 2010; Gelbard 2013; Mortensen 2021; Palmieri 2009; Soh 2010; Ziegelmann 2019) (see 'Overview of outcomes', Table 3). Further details including the

outcome measurement methods and timing can be found in Table 2 ('Study characteristics') and the Characteristics of included studies.

Funding sources and conflicts of interest

Six trials reported a funding source (Chitale 2010; Gelbard 2012; Gelbard 2013; Greenfield 2007; Weidner 2005; Ziegelmann 2019). Three trials reported no funding source (Antar 2019; Mortensen 2021; Palmieri 2009), and the remaining trials did not mention a funding source. Five trials reported a conflict of interest (Gelbard 2012; Gelbard 2013; Greenfield 2007; Hellstrom 2006; Ziegelmann 2019). Six trials reported no conflicts of interest (Chitale 2010; Hatzichristodoulou 2013; Moncada 2019; Mortensen 2021; Palmieri 2009; Soh 2010). The remaining trials did not mention conflicts of interest.

Excluded studies

We excluded 46 studies after evaluation of the full-text publications. Of these, 27 studies had the wrong comparators, one study had the wrong study population, eight studies were the wrong study designs, two were commentaries on an original article, one was a duplicate study, and six were excluded due to authenticity concerns. These retracted articles were all by the same author who has had to withdraw several studies because of fraud. We received approval to retract these studies from the Cochrane Urology editorial group and the Cochrane Cancer Network. The authors agreed to remove one study after expert opinion as the intervention of this study (injectional collagenase) was applied once at baseline (Gelbard 1993). We presented details of excluded studies in the Characteristics of excluded studies table.

Studies awaiting classification and ongoing trials

We found two ongoing trials that have not provided usable outcome data at this time (Ongoing studies).

We did not find any studies that we placed as awaiting classification (Characteristics of studies awaiting classification).

Risk of bias in included studies

For details, please refer to the Characteristics of included studies section, the risk of bias summary (Figure 2), and the risk of bias graph (Figure 3) for the main comparison.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Empty cell indicates that the outcome was not reported.

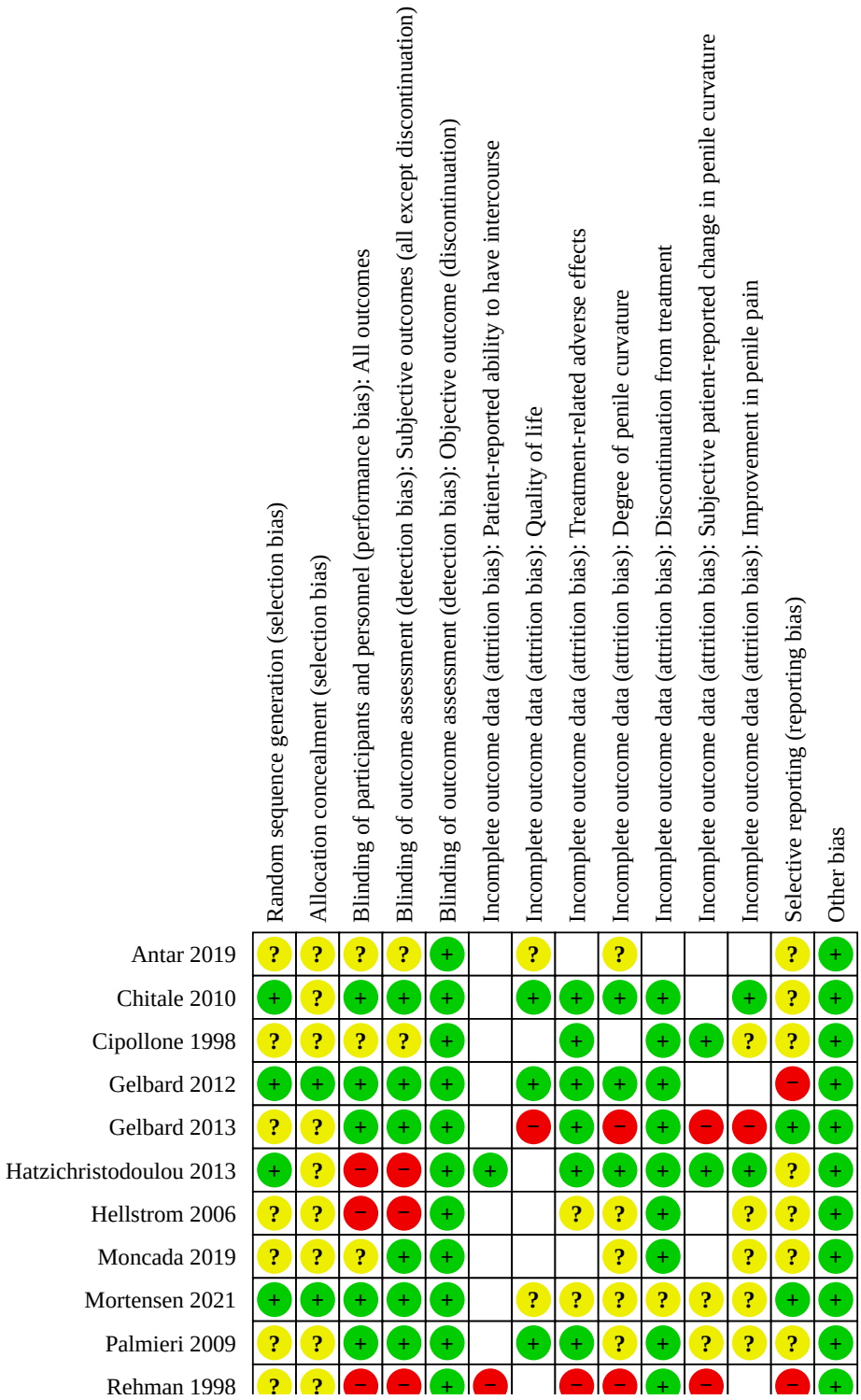


Figure 2. (Continued)

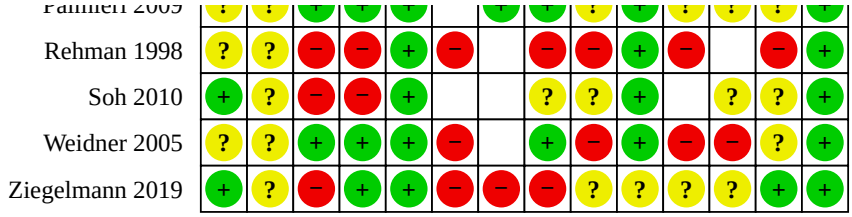
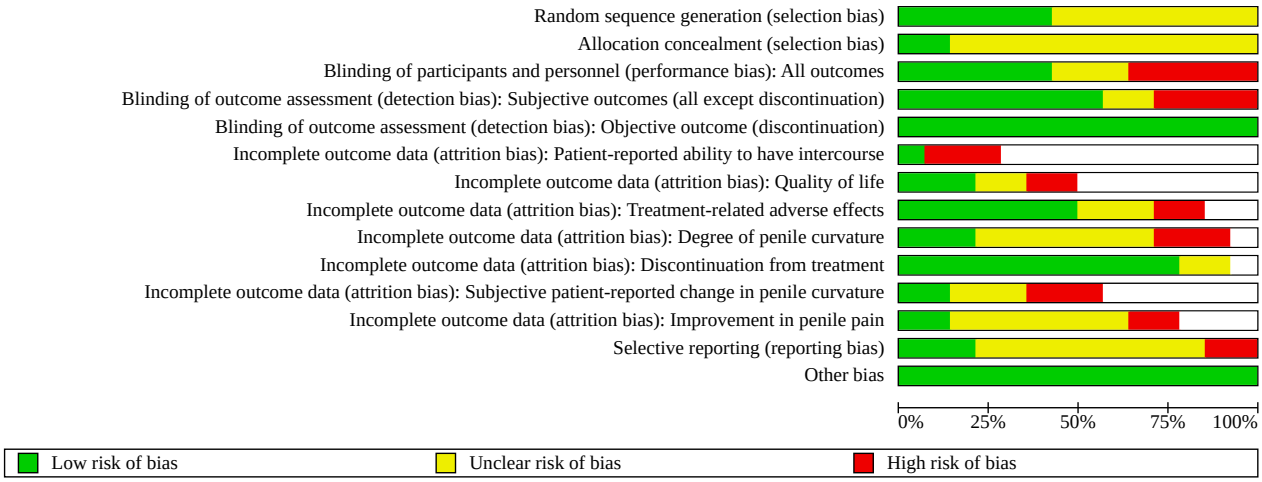


Figure 3.



Allocation

Random sequence generation

More than half of the trials (8/14) failed to report sufficient detail to provide assurance of an adequate method of sequence generation, and we rated them as having unclear risk of bias (Antar 2019; Cipollone 1998; Gelbard 2013; Hellstrom 2006; Moncada 2019; Palmieri 2009; Rehman 1998; Weidner 2005). Six trials reported an appropriate method, and we rated them as low risk (Chitale 2010; Gelbard 2012; Hatzichristodoulou 2013; Mortensen 2021; Soh 2010; Ziegelmann 2019).

Allocation concealment

We rated allocation concealment as unclear in all but two trials (2/14). Gelbard 2012 and Mortensen 2021 documented an appropriate method.

Blinding

Blinding of participants and personnel

We judged five studies as high risk (5/14) since these parties were not blinded (Hatzichristodoulou 2013; Hellstrom 2006; Rehman 1998; Soh 2010; Ziegelmann 2019). Six studies blinded both participants and personnel, and we rated them as having low risk of bias (6/14; Chitale 2010; Gelbard 2012; Gelbard 2013; Mortensen 2021; Palmieri 2009; Weidner 2005). We judged three studies as having an unclear risk of bias (3/14; Antar 2019; Cipollone 1998; Moncada 2019).

Blinding of outcome assessment

We distinguished between outcomes for which blinding of outcome assessors appears relevant ('subjective' outcomes) versus those for which it does not.

Subjective outcomes were patient-reported improvement in ability to have intercourse, quality of life, treatment-related adverse effects, degree of penile curvature, subjective patient-reported change in penile curvature, and improvement in penile pain (associated with curvature or plaque). We rated eight studies (8/14) as low risk of bias (Chitale 2010; Gelbard 2012; Gelbard 2013; Moncada 2019; Mortensen 2021; Palmieri 2009; Weidner 2005; Ziegelmann 2019). We rated four studies as having high risk of bias (Hatzichristodoulou 2013; Hellstrom 2006; Rehman 1998; Soh 2010), while we rated two studies as having unclear risk of bias (Antar 2019; Cipollone 1998).

Objective outcomes were discontinuation from treatment (for any cause). We rated all (14/14) studies at low risk for bias with regard to these outcomes because their measurement did not include any subjective judgment.

Incomplete outcome data

Patient-reported ability to have intercourse: Four studies reported this outcome. One study had low levels of attrition (less than 10% for both arms) that permitted a low risk of bias judgment (1/4; Hatzichristodoulou 2013). The three remaining

studies reported high levels of attrition for this outcome (20% or greater at least in one arm) and we rated them as high risk of bias (3/4; Rehman 1998; Weidner 2005; Ziegelmann 2019).

Quality of life: Seven studies reported this outcome. Three studies reported low rates of attrition that permitted a low risk of bias judgment (3/7; Chitale 2010; Gelbard 2012; Palmieri 2009). Two studies reported high levels of attrition for this outcome, and we rated them as high risk of bias (2/7; Gelbard 2013; Ziegelmann 2019), while we rated the remaining two as having an unclear risk of bias (Antar 2019; Mortensen 2021).

Treatment-related adverse effects: Nearly all studies (11/14) contributed data for this outcome. Six studies reported low levels of attrition that permitted a low risk of bias judgment (6/13; Chitale 2010; Cipollone 1998; Gelbard 2012; Gelbard 2013; Hatzichristodoulou 2013; Palmieri 2009). Two studies reported high levels of attrition for this outcome, and we rated them as high risk of bias (2/13; Rehman 1998; Ziegelmann 2019), while we rated the remaining three studies as having an unclear risk of bias(Hellstrom 2006; Mortensen 2021; Soh 2010).

Degree of penile curvature: This outcome was reported by most studies (12/14). Three studies had low levels of attrition that permitted a low risk of bias judgment (3/12; Chitale 2010; Gelbard 2012; Hatzichristodoulou 2013). Two studies reported high levels of attrition for this outcome, and we rated them as high risk of bias (2/12; Rehman 1998; Weidner 2005), while we judged the remaining (7/12) as having an unclear risk of bias.

Discontinuation from treatment: This outcome was reported by 13 studies. Eleven studies (11/13) reported low levels of attrition that permitted a low risk of bias judgment. We judged the remaining two studies as being at unclear risk of bias (Mortensen 2021; Ziegelmann 2019).

Patient-reported subjective improvement in penile curvature: Two of seven studies reporting this outcome had low levels of attrition that permitted a low risk of bias judgment (Cipollone 1998; Hatzichristodoulou 2013). Two studies reported high levels of attrition for this outcome, and we rated them as high risk of bias (2/7; Rehman 1998; Weidner 2005), while we rated the remaining three as unclear risk of bias.

Patient-reported improvement of pain: Among 11 studies addressing this outcome, two studies reported low levels of attrition that permitted a low risk of bias judgment (2/11; Chitale 2010; Hatzichristodoulou 2013). Two studies reported high levels of attrition for this outcome, and we rated them as high risk of bias (2/11; Gelbard 2013; Weidner 2005), while we judged the remaining studies to be at unclear risk of bias.

Selective reporting

We found *a priori* protocols for three included studies (3/14) (Gelbard 2013; Mortensen 2021; Ziegelmann 2019); these reported all pre-identified outcomes as planned in the protocol, and we judged them as low risk of bias. In total, we rated two studies as having high risk of bias due to apparent omissions of information (2/14; Gelbard 2012; Rehman 1998), while the rest were at unclear risk of bias because we have no assurance that all measured outcomes were reported and analyzed as planned.

Other potential sources of bias

We found no other sources of bias in any of the 14 included studies (0/14) and rated them all as low risk of bias.

Effects of interventions

See: **Summary of findings 1** Potassium paraaminobenzoate compared to placebo for Peyronie's disease (short-term); **Summary of findings 2** Injectional interferon alpha-2B compared to saline for Peyronie's disease (short-term); **Summary of findings 3** Injectional nicardipine compared to saline for Peyronie's disease (long-term); **Summary of findings 4** Injectional betamethasone compared to saline for Peyronie's disease (long-term); **Summary of findings 5** Injectional collagenase compared to placebo for Peyronie's disease (short-term); **Summary of findings 6** Injectional collagenase compared to placebo for Peyronie's disease (long-term); **Summary of findings 7** Injectional verapamil versus saline (short-term); **Summary of findings 8** Injectional Botox compared to placebo for Peyronie's disease (short-term); **Summary of findings 9** Extracorporeal shock wave treatment (ESWT) compared to sham for Peyronie's disease (short-term); **Summary of findings 10** Penile traction therapy versus no treatment (short-term)

1. Oral agents

1.1 Oral potassium paraaminobenzoate (POTABA) versus placebo (short-term)

See Summary of findings 1.

Patient-reported ability to have intercourse

Based on a single trial, POTABA may result in little to no difference in patient-reported ability to have intercourse (risk ratio (RR) 1.19, 95% confidence interval (CI) 0.87 to 1.62; 1 study, 75 participants; low certainty of evidence (CoE); Analysis 1.1) (Weidner 2005). This corresponds to 119 more (81 fewer to 388 more) men reporting the ability to have intercourse. We downgraded the CoE for serious study limitations and serious imprecision.

Quality of life

We found no evidence for this outcome.

Treatment-related adverse events

Based on a single trial, we are very uncertain how POTABA may affect treatment-related adverse events (RR 1.27, 95% CI 0.36 to 4.48; 1 study, 103 participants; very low CoE; Analysis 1.2) (Weidner 2005). We downgraded the CoE for serious study limitations and very serious imprecision.

Degree of penile curvature

We found no evidence for this outcome.

Discontinuation from treatment

Based on a single trial, we are very uncertain how POTABA may affect discontinuation from treatment (RR 1.36, 95% CI 0.72 to 2.58; 1 study, 103 participants; very low CoE ; Analysis 1.3) (Weidner 2005). We downgraded the CoE for serious study limitations and very serious imprecision.

Subjective patient-reported change in penile curvature

Based on a single trial we are very uncertain how POTABA may affect subjective patient-reported change in penile curvature (RR

1.07, 95% CI 0.72 to 1.58; 1 study, 62 participants; very low CoE; Analysis 1.4) (Weidner 2005). We downgraded the CoE for serious study limitations and very serious imprecision.

Improvement in penile pain

We found no evidence for this outcome.

2. Injectional agents

2.1 Injectional interferon alpha-2B versus saline (short-term)

See Summary of findings 2.

Patient-reported ability to have intercourse

We found no evidence for this outcome.

Quality of life

We found no evidence for this outcome.

Treatment-related adverse events

We found no evidence for this outcome.

Degree of penile curvature

Based on a single trial, we are very uncertain how interferon alpha-2B may affect degree of penile curvature (MD -10.00, 95% CI -15.95 to -4.05; 1 study, 103 participants; very low CoE; Analysis 2.1) (Hellstrom 2006). We downgraded the CoE for serious study limitations, serious indirectness (given that patients with more than one plaque were excluded from the trial), and serious imprecision.

Discontinuation from treatment

Based on a single trial, we are very uncertain how interferon alpha-2B may affect discontinuation from treatment (RR 0.63, 95% CI 0.22 to 1.76; 1 study, 117 participants; very low CoE; Analysis 2.2) (Hellstrom 2006). We downgraded the CoE for serious study limitations, serious indirectness (given that patients with more than one plaque were excluded from the trial), and very serious imprecision.

Subjective patient-reported change in penile curvature

We found no evidence for this outcome.

Improvement in penile pain

We found no evidence for this outcome.

2.2 Injectional nicardipine versus saline (long-term)

See Summary of findings 3.

Patient-reported ability to have intercourse

We found no evidence for this outcome.

Quality of life

We found no evidence for this outcome.

Treatment-related adverse events

Based on a single trial, we are very uncertain how injectional nicardipine may affect treatment-related adverse events (RR 2.82, 95% CI 0.12 to 66.62; 1 study, 62 participants; very low CoE; Analysis 3.1) (Soh 2010). No adverse events were reported in the control group. We downgraded the CoE for serious study limitations and very serious imprecision.

Degree of penile curvature

Based on a single trial, we are very uncertain how injectional nicardipine may affect the degree of penile curvature (MD -3.30, 95% CI -7.62 to 1.02; 1 study, 62 participants; very low CoE; Analysis 3.2) (Soh 2010). We downgraded the CoE for serious study limitations and very serious imprecision given that the 95% CI crosses the assumed threshold of a 25% change in curvature, which was 7.5 degrees.

Discontinuation from treatment

Based on a single trial, we are very uncertain how injectional nicardipine may affect discontinuation from treatment (RR 0.71, 95% CI 0.25 to 2.05; 1 study, 74 participants; very low CoE; Analysis 3.3) (Soh 2010). We downgraded the CoE for serious study limitations and very serious imprecision.

Subjective patient-reported change in penile curvature

We found no evidence for this outcome.

Improvement in penile pain

Based on a single trial, injectional nicardipine may result in little to no difference in penile pain (MD -0.21, 95% CI -0.38 to -0.04; 1 study, 62 participants; low CoE; Analysis 3.4) (Soh 2010). We downgraded the CoE for serious study limitations and serious imprecision.

2.3 Injectional betamethasone versus saline (long-term)

See Summary of findings 4.

Patient-reported ability to have intercourse

We found no evidence for this outcome.

Quality of life

We found no evidence for this outcome.

Treatment-related adverse events

Based on a single trial, we are very uncertain how betamethasone may affect treatment-related adverse events (RR not estimable, 1 study, 30 participants; very low CoE; Analysis 4.1) (Cipollone 1998). No adverse events were reported in either the treatment or control group. We downgraded the CoE for serious study limitations and very serious imprecision.

Degree of penile curvature

We found no evidence for this outcome.

Discontinuation from treatment

Based on a single trial, we are very uncertain how betamethasone may affect discontinuation from treatment (RR not estimable, 1 study, 30 participants; very low CoE; Analysis 4.2) (Cipollone 1998). No events were reported in either the treatment or control group. We downgraded the CoE for serious study limitations and very serious imprecision.

Subjective patient-reported change in penile curvature

Based on a single trial, we are very uncertain how injectional betamethasone may affect subjective patient-reported change

in penile curvature (RR 0.75, 95% CI 0.20 to 2.79; 1 study, 30 participants; very low CoE; Analysis 4.3) (Cipollone 1998). We downgraded the CoE for serious study limitations and very serious imprecision.

Improvement in penile pain

We found no evidence for this outcome.

2.4 Injectional collagenase versus placebo (short-term)

See Summary of findings 5.

Patient-reported ability to have intercourse

We found no evidence for this outcome.

Quality of life

Based on a single trial, injectional collagenase may result in little to no difference in quality of life short-term (MD -1.80, 95% CI -3.58 to -0.02; 1 study, 134 participants; low CoE; Analysis 5.1) (Gelbard 2012). Quality of life was assessed using the Peyronie's disease patient-reported outcome questionnaire with higher scores indicating worse quality of life on a scale from 0 to 20. We downgraded the CoE for serious study limitations and serious study imprecision given that the 95% CI crosses the assumed threshold of a 25% change in the baseline, which was 2 points.

Treatment-related adverse events

We found no evidence for this outcome.

Degree of penile curvature

Based on a single trial, injectional collagenase may result in little to no difference in the degree of penile curvature short-term (MD -10.90, 95% CI -16.24 to -5.56; 1 study, 136 participants; low CoE; Analysis 5.2) (Gelbard 2012). We downgraded the CoE for serious study limitations and serious imprecision given that the 95% CI crosses the assumed threshold of a 25% change in curvature, which was 12 degrees.

Discontinuation from treatment

We found no evidence for this outcome.

Subjective patient-reported change in penile curvature

We found no evidence for this outcome.

Improvement in penile pain

We found no evidence for this outcome.

2.5 Injectional collagenase versus placebo (long-term)

See Summary of findings 6.

Patient-reported ability to have intercourse

We found no evidence for this outcome.

Quality of life

Based on a single trial, injectional collagenase likely results in little to no difference in quality of life long-term (MD -1.00, 95% CI -1.60 to -0.40; 1 study, 612 participants; moderate CoE; Analysis 6.1) (Gelbard 2013). Quality of life was assessed with the Peyronie's disease questionnaire bother domain with a higher score indicating worse quality of life on a scale from 0 to 16. We downgraded the CoE for serious study limitations. The effect estimate was less than the assumed threshold of a 25% change from baseline of 1.9 points.

Treatment-related adverse events

Based on a single trial, injectional collagenase likely increases treatment-related adverse events long-term (RR 2.32, 95% CI 1.98 to 2.72; 1 study, 832 participants; moderate CoE; Analysis 6.2) (Gelbard 2013). This corresponds to 479 more per 1000 (356 more to 624 more) men experiencing treatment-related adverse events. The three most common adverse events in the collagenase group were penile ecchymosis, penile swelling, and penile pain. Six participants in the treatment group experienced serious adverse events, namely corporeal rupture (n = 3) and penile hematoma (n = 3). All ruptures and one of three hematoma cases required surgical interventions. We downgraded the CoE for serious study limitations.

Degree of penile curvature

Based on a single trial, injectional collagenase likely results in little to no difference in degree of penile curvature long-term (MD -6.90, 95% CI -9.64 to -4.16; 1 study, 612 participants; moderate CoE; Analysis 6.3) (Gelbard 2013). We downgraded the CoE for serious study limitations. The effect estimate is less than the assumed threshold of a 25% change in curvature, which was 12 degrees.

Discontinuation from treatment

Based on a single trial, we are very uncertain how injectional collagenase may affect discontinuation from treatment long-term (RR 1.25, 95% CI 0.84 to 1.86; 1 study, 836 participants; low CoE; Analysis 6.4) (Gelbard 2013). This corresponds to 27 more per 1000 (17 fewer to 92 more) men discontinuing treatment. We downgraded the CoE for serious study limitations and very serious imprecision.

Subjective patient-reported change in penile curvature

Based on a single trial, injectional collagenase likely improves subjective, patient-reported degree of penile curvature long-term (RR 2.07, 95% CI 1.66 to 2.59; 1 study, 612 participants; moderate CoE; Analysis 6.5) (Gelbard 2013). This corresponds to 314 more per 1000 (194 more to 467 more) men with subjectively perceived reduced curvature. We downgraded the CoE for serious study limitations.

Improvement in penile pain

Based on a single trial, injectional collagenase may result in little to no difference in penile pain long-term (MD -0.10, 95% CI -0.95 to 0.75; 1 study, 612 participants; low CoE; Analysis 6.6) (Gelbard 2013). We downgraded the CoE for serious study limitations.

2.6 Injectional verapamil versus saline (short-term)

See Summary of findings 7.

Patient-reported ability to have intercourse

Based on a single trial, we are very uncertain how injectional verapamil may affect self-reported ability to have intercourse (RR 7.00, 95% CI 0.43 to 114.70; 1 study, 14 participants; very low CoE; Analysis 7.1) (Rehman 1998). There were no events in the control group. We downgraded the CoE for serious study limitations and very serious imprecision.

Quality of life

We found no evidence for this outcome.

Treatment-related adverse events

Based on a single trial, we are very uncertain how injectional verapamil may affect treatment-related adverse events (very low CoE; Analysis 7.2) (Rehman 1998). There was no event in either group. We downgraded the CoE for serious study limitations and very serious imprecision.

Degree of penile curvature

Based on a single trial, we are very uncertain how injectional verapamil may affect degree of penile curvature (MD -1.86, 95% CI -10.39 to 6.67; 1 study, 14 participants; very low CoE; Analysis 7.3) (Rehman 1998). We downgraded the CoE for serious study limitations and serious imprecision given that the 95% CI crosses the assumed threshold of a 25% change in curvature, which was 8 degrees.

Discontinuation from treatment

We found no evidence for this outcome.

Subjective patient-reported change in penile curvature

Based on a single trial, we are very uncertain how injectional verapamil may affect subjective patient-reported change in penile curvature (RR 1.20, 95% CI 0.27 to 5.44; 1 study, 61 participants; very low CoE; Analysis 7.4) (Rehman 1998). We downgraded the CoE for serious study limitations and very serious imprecision.

Improvement in penile pain

We found no evidence for this outcome.

2.7 Injectional Botox (botulinum toxin unless specifying the brand name) versus placebo (short-term)

See Summary of findings 8.

Patient-reported ability to have intercourse

We found no evidence for this outcome.

Quality of life

Based on a single trial, we are very uncertain how injectional Botox may affect quality of life (MD 0.67, 95% CI -1.50 to 2.84; 1 study, 12 participants; very low CoE; Analysis 8.1) (Antar 2019). Quality of life was assessed using the International Index of Erectile Function questionnaire with a higher score indicating better quality of life on a scale from 0 to 5. Follow-up time was 16 weeks. We downgraded the CoE for serious study limitations and very serious imprecision given that the 95% CI crosses the assumed threshold of a 25% point change in quality of life, which was 1.2 points, on both sides of the confidence interval.

Treatment-related adverse events

We found no evidence for this outcome.

Degree of penile curvature

We found no evidence for this outcome.

Discontinuation from treatment

We found no evidence for this outcome.

Subjective patient-reported change in penile curvature

We found no evidence for this outcome.

Improvement in penile pain

We found no evidence for this outcome.

3. Device-based application

3.1 Extracorporeal shock wave treatment (ESWT) versus sham (short-term)

See Summary of findings 9.

Patient-reported ability to have intercourse

Based on a single trial, we are very uncertain how ESWT may affect self-reported ability to have intercourse (RR 1.60, 95% CI 0.71 to 3.60; 1 study, 26 participants; very low CoE; Analysis 9.1) (Hatzichristodoulou 2013). We downgraded the CoE for serious study limitations and very serious imprecision.

Quality of life

Based on two trials, ESWT may result in little to no difference in quality of life (MD 3.10, 95% CI 1.57 to 4.64; 2 studies, 130 participants; I^2 = 0%; low CoE; Analysis 9.2) (Mortensen 2021; Palmieri 2009). We downgraded the CoE for serious study limitations and serious imprecision given that the 95% CI crosses the assumed threshold of a 25% change in quality of life score, which was 4 points.

Treatment-related adverse events

Based on three trials, we are very uncertain how ESWT may affect treatment-related adverse events (RR 2.73, 95% CI 0.74 to 10.14; 3 studies, 166 participants; I^2 = 0%; very low CoE; Analysis 9.3) (Chitale 2010; Mortensen 2021; Palmieri 2009). We downgraded the CoE for serious study limitations and very serious imprecision with a very wide confidence interval assuming a threshold of clinical importance of a 25% relative change.

Degree of penile curvature

Based on three trials, ESWT may result in little to no difference in penile curvature (MD -2.84, 95% CI -7.35 to 1.67; 2 studies, 166 participants; I^2 = 37%; low CoE; Analysis 9.4) (Chitale 2010; Mortensen 2021; Palmieri 2009). We downgraded the CoE for serious study limitations and serious imprecision given that the 95% CI crosses the assumed threshold of a 25% change in curvature, which was 7 degrees, and the small overall sample size.

Discontinuation from treatment

Based on four trials, we are very uncertain how ESWT may affect discontinuation from treatment (RR 0.57, 95% CI 0.06 to 5.65; 4 studies, 268 participants; very low CoE; Analysis 9.5) (Chitale 2010; Hatzichristodoulou 2013; Mortensen 2021; Palmieri 2009). We downgraded the CoE for serious study limitations and very serious imprecision with a very wide confidence interval assuming a threshold of clinical importance of a 25% relative change.

Subjective patient-reported change in penile curvature

Based on two trials, we are very uncertain how ESWT affects subjective patient-reported change in penile curvature (RR 1.16, 95% CI 0.72 to 1.87; 2 studies, 129 participants; very low CoE; Analysis 9.6) (Hatzichristodoulou 2013; Mortensen 2021).

We downgraded the CoE for serious study limitations and very serious imprecision given the small sample size and width of the confidence interval.

Improvement in penile pain

Based on three trials, ESWT may improve penile pain (MD -1.09, 95% CI -2.22 to 0.04; 3 studies, 151 participants; I^2 = 59%; low CoE; Analysis 9.7) (Chitale 2010; Mortensen 2021; Palmieri 2009). We downgraded the CoE for serious study limitations and serious imprecision given that the 95% CI crosses the assumed MCID threshold of a one-point reduction on a 10-point VAS.

3.2 Penile traction therapy versus control (short-term)

See Summary of findings 10.

Patient-reported ability to have intercourse

We found no evidence for this outcome.

Quality of life

Based on a single trial, we are very uncertain how penile traction therapy effects quality of life (MD -1.50, 95% CI -3.42 to 0.42; 1 study, 82 participants; very low CoE; Analysis 10.1) (Ziegelmann 2019). We downgraded the CoE for serious study limitations and very serious imprecision given that the 95% CI crosses the assumed threshold of a 25% change in quality of life score, which was 2.2 points, as well as the small study size.

Treatment-related adverse events

Based on one trial, we are very uncertain how penile traction therapy may affect treatment-related adverse events (very low CoE; Analysis 10.2) (Ziegelmann 2019). There was no event in either group. We downgraded the CoE for serious study limitations and very serious imprecision.

Degree of penile curvature

Based on a single trial, we are very uncertain how penile traction therapy effects the degree of penile curvature (MD -7.40, 95% CI -11.18 to -3.62; 1 study, 89 participants; very low CoE; Analysis 10.3) (Ziegelmann 2019). We downgraded the CoE for serious study limitations and very serious imprecision given that the 95% CI crosses the assumed threshold of a 25% change in curvature, which was 11 degrees, and the small study size.

Discontinuation from treatment

Based on two trials, we are very uncertain how penile traction therapy may affect discontinuation from treatment (RR 0.86, 95% CI 0.31 to 2.36; 2 studies, 182 participants; very low CoE; Analysis 10.4) (Moncada 2019; Ziegelmann 2019). We downgraded the CoE for serious study limitations and very serious imprecision.

Subjective patient-reported change in penile curvature

We found no evidence for this outcome.

Improvement in penile pain

Based on a single trial, we are very uncertain how penile traction therapy affects improvement in penile pain (MD -0.60, 95% CI -2.28 to 1.08; 1 study, 82 participants; very low CoE; Analysis 10.5) (Ziegelmann 2019). We downgraded the CoE for serious study limitations and very serious imprecision given that the 95% CI crosses the assumed threshold of a 25% improvement in baseline penile pain score, which was 0.7, on both sides.

DISCUSSION

Summary of main results

This review identified 14 unique randomized controlled trials (RCTs) informing 10 distinct comparisons of non-surgical interventions for Peyronie's disease compared to sham and/or placebo. Comparisons with relevant outcome data were mostly informed by single trials. These related to oral agents (n = 1), injectional agents (n = 7), and device-based applications (n = 2). For all but three interventions only short-term (up to six months after end of treatment) outcome data were available. Many patient-important outcomes were not reported and for the majority of comparisons and outcomes the certainty of evidence (CoE) was very low. We were unable to establish that any of the included non-surgical interventions improved patient-reported ability to have intercourse, quality of life, or degree of curvature.

Overall completeness and applicability of evidence

This systematic review represents the most rigorous and up-to-date review on the question of non-surgical treatment of Peyronie's disease. Although we perceive this body of evidence to be broadly applicable to current clinical practice, the following issues deserve mention.

- The trials informing this review originate from many different countries therefore increasing the applicability of its findings. However, most comparisons were only informed by a single trial, therefore lacking documented reproducibility. In accordance with current GRADE guidance we did not use this as a reason to downgrade these findings (further) but recognize that other frameworks for rating the CoE, such as that used by the Agency for Healthcare, Research and Quality, would label the evidence from single trials as "insufficient"(AHRQ Methods 2015).
- The explicit scope of this review was to assess the effect of the included non-surgical interventions compared to placebo/sham or no treatment, not to compare different presumably active interventions with each other.
- The inclusion and exclusion criteria of individual trials included in this review varied considerably (as reflected in Table 1 and Table 2) making it difficult to compare therapies to each other in different stages of disease. We also noted that many of the trials are quite dated and were published over 20 years ago. However, given that we compared all interventions to placebo and that the standard of care has changed little over time, this should matter less than the documented lack of methodological rigor of many of these studies.
- This review initially included a number of interventions that are no longer widely used in most countries, in particular North America and Europe. We narrowed down the scope of the review as described in the protocol (Pagliara 2016), by surveying an external group of content experts. We recognize that we also excluded interventions such as non-steroidal antiinflammatory agents (NSAIDs), which have their main use in the acute disease stage in the treatment of pain, or phosphodiesterase-5 inhibitors, which are mainly used to treat the concomitant issues of erectile dysfunction (Manka 2021). We also did not include platelet-rich plasma as an intervention for which we found a

single trial (Chu 2022). This intervention is being explored as the topic of a separate Cochrane Review.

- Our search identified several trials by an Iranian author with five withdrawn publications in the arena of men's health due to documented fraud (Safarinejad 2004; Safarinejad 2007; Safarinejad 2009; Safarinejad 2010a; Safarinejad 2010b; Shirazi 2009), according to the Retraction Watch database (Retraction Watch Database). All these potentially eligible trials had serious limitations and small sample size and were the only trials informing these comparisons. Given major concerns about the veracity of these data, we made the decision in consultation with the Editorial Group (Cochrane Urology) and the Cochrane Cancer Network to exclude these studies.
- Clinically, the degree of curvature and disease stage (active versus latent) are important. We therefore predefined subgroup analyses to assess their impact and identify potential interactions. Given the paucity of data available, none of these secondary analyses could be performed.
- Recent studies have raised concerns about the long-term risk of penile rupture following treatment with injectional collagenase. Yafi 2018 conducted a survey of physician prescribers and found that approximately one in three had experienced this complication. Beilan 2018 reported a series of 105 patients of whom 4.9% developed penile rupture, most of whom underwent surgical repair. Given the lack of long-term comparative studies this specific serious adverse event is likely not fully appreciated in this review.
- GRADE guidance describes the use of non-randomized evidence as complementary to that of RCTs in settings where the body of RCT evidence is only of low or very low certainty, as in our case (Schünemann 2013). Although it is possible that comparative non-RCT evidence exists that might have contributed higher-quality evidence to this review, this appears unlikely.

Quality of the evidence

For those outcomes for which there was evidence, we mostly rated the CoE as very low due to issues relating to several of the GRADE domains. The most common issue were as follows:

- Study limitations: the method of random sequence generation and, more importantly, allocation concealment was unclear for the vast majority of studies raising concerns about selection bias. For many comparisons and outcomes there were also issues relating to at least one of the following, namely blinding of patients and personnel (performance bias), blinding of outcome assessors (detection bias), and failure to include a majority of randomized participants in the analyses (attrition bias). We also failed to identify an *a priori* protocol for all but three of the included studies (unclear or high risk of selection bias). As a result we downgraded all outcomes at least once for study limitations.
- Most analyses included few participants and had few events, resulting in wide confidence intervals that crossed predefined thresholds of importance for clinical decision-making, thereby promoting us to downgrade for serious or very serious imprecision.
- As highlighted in a recent literature review (Piraino 2022), we also found that included studies were inconsistent in how they defined acute and later phase stages of Peyronie's disease and to what extent acute phase participants were excluded. This issue is a potential source of indirectness, although we chose not to downgrade the certainty of evidence further in any comparison.

Potential biases in the review process

The study was performed based on rigorous Cochrane standards, which included a published protocol (Pagliara 2016). Nevertheless, certain issues could be a source of bias.

- We performed a comprehensive literature search for eligible studies irrespective of language and publication status. Nevertheless, we may have missed studies, in particular 'negative' studies published in languages other than English. This may have resulted in publication bias that we were unable to assess with statistical approaches, such as funnel plots, given the paucity of included studies by comparison.
- Included studies reported participants' outcomes at different time points. To provide meaningful summary data that might be helpful for clinicians and patients, we grouped the available data by two time periods of short-term and long-term. Short-term was defined as within six months after end of treatment and long-term was defined as over six months after end of treatment. These categories were established with input by expert clinicians after the protocol was written, and the data were abstracted, but before any quantitative analysis was performed. Nevertheless, findings for these outcomes are potentially sensitive to the specific time ranges we chose, and this may be viewed as a potential source of bias.
- Interpretation of our results very much hinges on the choice of what constitutes a minimally clinically important difference (MCID). In the absence of published thresholds for the outcomes of this review, we used a 25% risk reduction or increase as a threshold, based on published methodological guidance (Guyatt 2011a). Applying this threshold, none of the interventions, including collagenase, met the MCID threshold. Since that time, Ziegelmann 2017 has suggested that a 10% improvement in the degree of curvature from baseline might be considered clinically meaningful. Had we applied this lower MCID, we would have concluded that injectional collagenase may improve penile curvature both short term and long term, although to a small degree. It should be noted that this study, conducted by the investigators of the collagenase study that led to the agent's approval by the US Food and Drug Administration (FDA), was based only on a subset of patients and that this proposed threshold has not been externally validated. Our use of a 25% relative risk reduction/increase as threshold was consistent with our published protocol (Pagliara 2016).
- It may also be noteworthy that the focus of this review was the comparative effectiveness of various agents to placebo, sham, or usual treatment. While participants' response, for example in terms of curvature improvement, may have been greater than our data suggests, that is because some improvement was also seen in those participants that did not receive the active intervention.

Agreements and disagreements with other studies or reviews

To date, no review has applied the rigorous Cochrane methodology to this topic. Defining characteristics of this review include an a priori protocol, a comprehensive literature search irrespective of language and publication status, a focus on patient-

centered outcomes, and the application of GRADE methodology. Furthermore, our interpretation focuses on clinically relevant (rather than statistically significant) findings and provides absolute effect size estimates for all dichotomous outcomes.

- Russo 2018 is a protocol-driven systematic review of various injection and mechanical therapies for Peyronie's disease that included both randomized and non-randomized studies. The study did not conduct any meta-analyses, and it is unclear whether they conducted any effect size analyses on their own. Risk of bias was assessed on a study, not outcome, level and the review failed to provide any CoE rating to place their findings into perspective. In their conclusions they highlight their findings that injectional collagenase and interferon alpha-2b can decrease penile curvature. Our findings on collagenase correspond to the findings by Russo 2018 for this outcome while qualifying the CoE as moderate and also identifying an increase in treatment-related adverse events long-term; treatment-related harms were not addressed by Russo 2018. For interferon alpha-2b, we found the CoE to be very low and would also like to note that the two separate RCTs cited by Russo 2018 refer to the same single study summarized here as Hellstrom 2006.
- Russo 2019 is a network meta-analysis comparing injectional collagenase, verapamil, interferon a-2b, and hyaluronic acid (non-randomized) against placebo in the treatment of Peyronie's disease, with 1050 participants. This study also omitted an assessment of potential treatment-related harm, pooled across randomized and non-randomized trials, and included the publications we summarize under Hellstrom 2006 as two separate studies. While the author cites the use of GRADE for network meta-analysis, no CoE ratings were provided.
- Pyrgidis 2021 is a systematic review that investigated a broad scope of non-surgical interventions, many of which we excluded (as detailed above) due to limited contemporary relevance. They included both randomized and non-randomized trials. Whereas they assessed the risk of bias of the included studies, they failed to rate the certainty of evidence on a per-outcome basis. For most interventions, they provided narrative description of single study results. For select interventions and outcomes informed by more than one comparative study (for example, for collagenase injection plus adjunctive mechanical therapy versus injection therapy) they elected to indiscriminately pool across randomized and non-randomized trials, which defies basic principles of evidence-based medicine and contemporary methodological guidance and is therefore ill-advised.
- Bakr 2021 is a systematic review and meta-analysis focused on shock wave therapy. One fundamental limitation of this review was the lack of an a priori protocol as well as failure to provide references for those studies excluded at the full-text level; both of these being critical domains of the revised A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2) instrument (Shea 2017), the confidence we have in this review is that of "critically low". The review included the same three trials we identified (Chitale 2010; Hatzichristodoulou 2013; Palmieri 2009), but did not assess the certainty of evidence for the pooled effect estimates. They concluded that shock wave therapy fails to improve penile curvature or pain in men with Peyronie's disease but may reduce plaque size, which they interpret as being of questionable clinical significance. This concurs with our determination at our protocol stage to not include this outcome given its limited clinical relevance (Pagliara 2016).
- El-Sakka 2021 is a systematic review addressing a broad spectrum of medical, non-invasive, and minimally invasive treatment modalities for Peyronie's disease. It lacked an a priori protocol, applied a limited search strategy, and did not conduct risk of bias assessments on a per outcome level. One included study is represented twice in risk of bias tables (Favilla 2017). Given its methodological shortcomings, which included the absence of any certainty of evidence rating, its contribution to this topic is limited.
- Alkandari 2022 is a self-described systematic review focused on platelet-rich plasma (PRP) for the treatment of Peyronie's disease and erectile dysfunction. The study suffers from many of the same methodological limitations as Bakr 2021 and ultimately only provides a narrative review on the topic across study designs from animal studies to single-armed cohort studies to randomized controlled trials. They found a single trial on erectile dysfunction (which was outside the scope of this review), but none on Peyronie's disease.
- Existing guidelines from various professional societies such as those of the American Urological Association (Nehra 2015), the European Association of Urology (EAU) (Salonia 2021), the Canadian Urological Association (CUA) (Bella 2018), the French Urological Association (Ferretti 2021), and the International Society for Sexual Medicine (ISSM) (Chung 2016) frequently provide inconsistent guidance (as reviewed in Manka 2021), which, in light of our review findings, does not appear well-supported by evidence and may also underscore limitations in their guideline development process (Dahm 2017).
  - For example, guidelines by the European Association of Urology recommend against oral potassium paraaminobenzoate (Salonia 2021), whereas AUA and CUA guidelines consider it an option. Our review failed to demonstrate evidence of effectiveness.
  - The AUA, EAU, and ISSM agree that ESWT should not be used for the reduction of penile curvature, but suggest offering it to improve penile pain (Chung 2016; Nehra 2015; Salonia 2021). Our review did not address the outcome of pain (which relates to the acute phase of Peyronie's disease), but also found no evidence of effectiveness.
  - AUA, CUA, EAU, and ISSM all, with different qualifiers, see a role for penile traction therapy in the treatment of Peyronie's disease (Chung 2016; Chung 2016; Nehra 2015; Salonia 2021). A recent position statement by the European Society for Sexual Medicine also indicated that there was not enough evidence to warrant a treatment recommendation (Garcia-Gomez 2021). The findings of our review mainly highlight the high degree of uncertainty as it relates to its impact on patient-important outcomes.
  - The EAU guideline recommends against intralesional verapamil (Salonia 2021), whereas the ISSM (Chung 2016) and AUA guidelines (Nehra 2015) see a potential role. All three guidelines also indicate that injectional interferon alpha-2B may be offered to patients with Peyronie's disease, as does the CUA (Bella 2018), while emphasizing side effects such as flu-like symptoms and sinusitis (Manka 2021).
  - Injectional collagenase receives recommendations (of differing strength) from the EAU (Salonia 2021), ISSM (Chung 2016), and the American Urological Association

(AUA) guidelines (Nehra 2015) as a non-surgical treatment of stable Peyronie's disease with penile curvature > 30° and < 90° and intact erectile function (with or without the use of medications). Our review highlights the relatively modest benefits and adverse events, which may help inform future guideline updates as well as shared decision-making between clinicians and patients.

AUTHORS' CONCLUSIONS

Implications for practice

There is a paucity of evidence supporting the effectiveness of non-surgical treatments for Peyronie's disease. Existing trials are mostly of poor methodological quality and/or fail to address patient-important outcomes. Our findings suggest some limited efficacy of oral potassium paraaminobenzoate, injectional collagenase, and extracorporeal shock wave treatment (ESWT) in improving select outcomes. Among these, collagenase has garnered the greatest commercial interest and may have reduced the number of patients undergoing surgical interventions (Sukumar 2020). It was recently pulled from the European market for unclear reasons (Cocci 2019), but remains available in the United States. Intracavernosal collagenase probably improves penile curvature, but only to a degree that many individuals may not perceive as clinically relevant, with the trade-off of increased adverse events.

Whereas it is explicitly outside the scope of this review to make any clinical recommendations, clinicians should share with their patients the very limited evidence on non-surgical treatments being effective interventions to inform a shared decision-making process about their use.

We further hope that this systematic review may serve as the common evidence base for future guideline efforts of the three leading organizations, the American Urological Association (AUA), European Association of Urology (EAU), and International Society for Sexual Medicine (ISSM), thereby avoiding duplication of effort towards de novo evidence synthesis and leading to more consistent and evidence-based recommendations.

Implications for research

The findings of this review underscore the need for higher-quality research with longer follow-up. Specifically, most studies fail to implement methodological safeguards against bias (such as allocation concealment) that are relevant to all clinical trials. Moreover, participants, personnel, and outcome assessors should be blinded whenever possible. Participant screening, enrollment, trial conduct, and analysis should follow an a priori protocol and every effort should be made to account for every randomized participant in the analysis. Many of these issues have recently been highlighted by Ziegelmann 2020 in a dedicated review article on the challenges of designing studies in this disease setting and evaluating outcomes. Specific issues raised include the lack of standardized protocols for pre- and post-intervention assessments, inter-observer and intra-observer variability in outcome assessment, and the lack of consistent definitions for what defines an objective outcome as clinically meaningful for patients. Christiansen 2021 also recently highlighted that most Peyronie's disease-related research is self-funded with only a small percentage from the National Institutes of Health (NIH) or industry.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Antar 2019

Study characteristics	
Methods	**Study design:** randomized, placebo-controlled **Setting/country:** likely single-center, USA **Dates when study was conducted:** NA
Participants	**Inclusion criteria:** stable phase PD **Exclusion criteria:** active PD, multiple plaques, calcified plaques **Total number of participants randomly assigned:** 12 **Group A:** • Number of participants randomly assigned: 6 • Age (years): NA • Disease duration (years): NA • Degree of penile curvature (degrees): NA • Number and size of plaques: NA **Group B:** • Number of participants randomly assigned: 6 • Age (years): NA • Disease duration (years): NA • Degree of penile curvature (degrees): NA • Number and size of plaques: NA
Interventions	**Group A:** injectional botulinum toxin type A **Group B:** placebo **Intervention duration:** 16 weeks **Follow-up (including intervention duration):** 16 weeks

Antar 2019 *(Continued)*

	Run-in period: NA
Outcomes	**Primary outcome** • Erectile function • Change in degree of penile curvature How measured: IIEF scores Time points measured: week 1, week 16 Time points reported: week 1, week 16 **Secondary outcome** • NA How measured: NA Time points measured: NA Time points reported: NA
Funding sources	None
Declarations of interest	Not described
Notes	**Funding sources:** none **Declarations of interest:** NA **Protocol:** none **Language of publication:** English Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgment: not described
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgment: not described
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Unclear risk	Judgment: not described
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding

Antar 2019 *(Continued)*

Incomplete outcome data (attrition bias) Quality of life	Unclear risk	Judgment: not described
Incomplete outcome data (attrition bias) Degree of penile curvature	Unclear risk	Judgment: not described
Selective reporting (reporting bias)	Unclear risk	Judgment: protocol was not available, and the review outcomes were not prespecified (abstract only)
Other bias	Low risk	Judgment: no additional biases detected

Chitale 2010

Study characteristics	
Methods	**Study design:** parallel RCT **Setting/country:** likely outpatient/single institute/UK **Dates when study was conducted:** NR
Participants	**Inclusion criteria:** men with stable penile deformity secondary to PD affecting their ability to perform sexual intercourse and/or quality of life due to penile angulation; recent onset of painless deformity of the penis on erection, and stable for > 6 months; pain and/or angulation of the penis on erection; difficult intercourse due to penile curvature, and partner dissatisfaction; a degree of erectile dysfunction (partial) associated with penile deformity; palpable plaque along the penis with penile deformity; aged > 18 years **Exclusion criteria:** men with congenital curvature of the penis; previous treatment for PD (surgical/medical); patient on warfarin; patient with total erectile dysfunction in need of therapy for erectile dysfunction **Total number of participants randomly assigned:** 36 **Group A** • Number of all participants randomly assigned: 16 • Age (years): 57.8 ± 8.0 • Disease duration: 14.9 ± 8.4 • Degrees penile curvature (degrees): 24.9 ± 11.9 • Number and size of plaques (cm^3): NR **Group B** • Number of all participants randomly assigned: 20 • Age (years): 60.0 ± 10.5 • Disease duration: 32.3 ± 28.0 • Degrees penile curvature (degrees): 33.3 ± 15.9 • Number and size of plaques (cm^3): NR
Interventions	**Group A:** limited shock wave therapy: treatment session (12 min when 3000 SWs were delivered at level 25 (38 MPa)) per week for 6 weeks **Group B:** sham therapy: same number of shock waves were delivered to those in the sham group but at level 0, with the SW generator still making the same clicking noise as during real shock wave therapy

Chitale 2010 *(Continued)*

	Intervention duration: 6 weeks **Follow-up (including intervention duration):** 6 months after treatment **Run-in period:** none
Outcomes	• Disappearance of pain • Palpatory reduction of about half the volume and the consistency of plaque • Subjective reduction of recurvatum How measured: patient satisfaction survey Time points measured: NR Time points reported: at baseline and 12 months **Safety outcome:** adverse event How measured: NR Time points measured: NR Time points reported: likely cumulative incidence **Subgroup:** none
Funding sources	Acknowledgment: we sincerely thank Mr Tony Dempster, Director, Focus Medical Services and his team for their immense help in conducting this trial
Declarations of interest	None
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgment: "randomized using computer generated numbers"
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgment: "same number of shock waves were delivered to those in the sham group but at level 0, with the shock wave generator still making the same clicking noise"
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Low risk	Judgment: "The assessor was also unaware of the type of treatment rendered until after completing the assessment. Only the technician operating the SW generator was aware of the type of treatment"
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding

Chitale 2010 *(Continued)*

Incomplete outcome data (attrition bias) Quality of life	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Degree of penile curvature	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Improvement in penile pain	Low risk	Judgment: all participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Judgment: while the review outcomes were prespecified in the methods, a protocol was not available
Other bias	Low risk	Judgment: no additional biases detected

Cipollone 1998

Study characteristics	
Methods	**Study design:** parallel RCT **Setting/country:** likely outpatient/single institute/Italy **Dates when study was conducted:** October 1995 to September 1996
Participants	**Inclusion criteria:** NR **Exclusion criteria:** men with presence of peptic ulcer, acute gastritis or esophagitis, diabetes mellitus, osteoporosis, glaucoma, cataract, severe arterial hypertension, and cardiovascular insufficiency **Total number of participants randomly assigned:** 30 • Age (years): 55 • Disease duration (months): 4 to 8 • Degrees penile curvature (degrees): NA • Number and size of plaques (mm): single plate of 8 to 15 The baseline characteristics of each group were not reported
Interventions	**Group A:** betamethasone infiltrative therapy, 2 mL/every 2 weeks **Group B:** isotonic saline solution infiltrative therapy, 2 mL/every 2 weeks **Intervention duration:** 24 weeks

Cipollone 1998 *(Continued)*

	Follow-up (including intervention duration): 12 months **Run-in period:** none
Outcomes	• Disappearance of pain • Palpatory reduction of about half the volume and the consistency of plaque • Subjective reduction of recurvatum How measured: patient satisfaction survey Time points measured: NR Time points reported: at baseline and 12 months **Safety outcome:** adverse event How measured: NR Time points measured: NR Time points reported: likely cumulative incidence **Subgroup:** none
Funding sources	NR
Declarations of interest	NR
Notes	**Protocol:** NA **Language of publication:** Italian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgment: not described
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgment: not described
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Unclear risk	Judgment: not described
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias)	Low risk	Judgment: all participants were included in the analysis

Cipollone 1998 *(Continued)*

Treatment-related adverse effects		
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Improvement in penile pain	Unclear risk	Judgment: no information (not measured)
Selective reporting (reporting bias)	Unclear risk	Judgment: protocol was not available
Other bias	Low risk	Judgment: no additional biases detected

Gelbard 2012

Study characteristics	
Methods	**Study design:** phase 2b, double-blind, randomized, placebo-controlled study **Setting/country:** likely outpatient/12 sites/USA **Dates when study was conducted:** NR
Participants	**Inclusion criteria:** healthy, heterosexual men over age 18 in a stable relationship with a partner/spouse (for at least 3 months), diagnosis of PD for at least 6 months, penile curvature of at least 30 degrees in the dorsal, lateral or dorsal/lateral plane (must have been possible to delineate the single plane of maximal curvature for evaluation), functional difficulty related to PD (e.g. erectile dysfunction or difficulty with intromission), signed informed institutional review board approved consent agreement **Exclusion criteria:** men with penile curvature of less than 30 or greater than 90 degrees, calcified plaque as evident by appropriate radiographic evaluation, penile X-ray or penile ultrasound (noncontiguous stippling was allowed), isolated hourglass malformation of the penis without curvature, plaque causing curvature of the penis located proximal to the base of the penis (injection of the local anesthesia would have interfered with the injection of collagenase *Clostridium histolyticum* into the plaque), severe pain during penile palpation (as determined by the investigator), allergy to collagenase or other medication required by the protocol, average of 3 successive blood pressure readings of 160/100 mmHg or greater during screening or the day 1 assessments, any conditions affecting the penis, such as thrombosis of the dorsal penile artery or chordee in the presence or absence of hypospadias, or erectile dysfunction that was unresponsive to phosphodiesterase type 5 inhibitors, and men who had received treatment or planned to undergo treatment for PD, including but not limited to any previous surgery, oral agents within 4 weeks, injectional medical therapies within 3 months, or use of mechanical devices within 2 weeks before the start of the study, does not respond with full erection to prostaglandin E1 during malformation measurement **Total number of participants randomly assigned:** 147

Gelbard 2012 *(Continued)*

	Group A • Number of all participants randomly assigned: 111 • Age (years): 56.98 ± 7.79 • Disease duration (years): 3.00 ± 3.12 • Degrees penile curvature (degrees): 54.4 ± 15.1 • Number and size of plaques: NR **Group B** • Number of all participants randomly assigned: 36 • Age (years): 55.4 ± 6.94 • Disease duration (years): 2.14 ± 2.95 • Degrees penile curvature (degrees): 50.6 ± 15.1 • Number and size of plaques: NR
Interventions	**Group A:** collagenase *Clostridium histolyticum* 2 injectional injections (interval of 24 to 72 hours between the injections) followed by 3 treatment cycles (6-week intervals) with 0.58 mg or 10,000 U per injection **Group B:** placebo with same schedule of group A **Intervention duration:** 18 weeks **Follow-up (including intervention duration):** 36 weeks **Run-in period:** none
Outcomes	• Penile curvature • Total score for each PD patient-reported outcome domain How measured: a goniometer protractor after injection of prostaglandin E1 to induce erection/PD patient-reported outcome questions were grouped into domains, including intercourse discomfort and constraint, penile pain, and PD symptom bother Time points measured: NR Time points reported: at baseline, 6, 18, and 36 weeks/at baseline and 36 weeks **Safety outcome:** adverse event incidence, and the change from baseline in laboratory values and vital signs How measured: treatment emergent when observed at any time after the first dose of injection Time points measured: whenever reported Time points reported: cumulative incidence **Subgroup:** stratified randomization according to PD remodeling (gradual, gentle stretching of the flaccid penis in the opposite direction of the curvature)
Funding sources	Auxilium Pharmaceuticals
Declarations of interest	Allergan, Auxilium, Biospecifics, Coloplast, Lilly, Astellas, Pfizer, American Medical Systems, and Repros Therapeutics
Notes	**Protocol:** NA **Language of publication:** English
Risk of bias	

Gelbard 2012 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized into 4 groups using the Interactive Web Response Services randomization computer system"
Allocation concealment (selection bias)	Low risk	Quote: "All investigators were assigned in blinded fashion to active vs placebo treatment using the Interactive Web Response Services program and given drug kits that were visually identical"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blinded placebo controlled study" Judgment: placebo-controlled study/participants and personnel were likely blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Low risk	Quote: "Double blinded placebo controlled study" Judgment: placebo-controlled study/outcome assessor was likely blinded
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Quality of life	Low risk	Judgment: 100/111 (90.0%) and 34/36 (94.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Degree of penile curvature	Low risk	Judgment: 100/111 (90.0%) and 34/36 (94.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Selective reporting (reporting bias)	High risk	Judgment: protocol was not available and the outcomes that were measured at different time points were omitted
Other bias	Low risk	Judgment: not detected

Gelbard 2013

Study characteristics	
Methods	**Study design:** prospective, multi-institutional, double-blind, randomized, placebo-controlled study **Setting/country:** likely outpatient/64 sites/USA and Australia **Dates when study was conducted:** September 2010 to March 2012

Gelbard 2013 *(Continued)*

Participants	**Inclusion criteria:** healthy men age 18 or older in a stable relationship with a female partner/spouse (for at least 3 months) and willing to have vaginal intercourse with that female partner/spouse, diagnosis of PD for at least 12 months with evidence of stable disease as determined by the investigator, penile curvature of at least 30° in the dorsal, lateral, or dorsal/lateral plane (must have been possible to delineate the single plane of maximal curvature for evaluation), signed informed Institutional Review Board-approved consent agreement; signed authorization form to allow disclosure of protected health information, ability to read, complete, and understand the various rating instruments in English **Exclusion criteria:** men with penile curvature of < 30° or > 90°, any conditions affecting the penis, such as chordee in the presence or absence of hypospadias; thrombosis of the dorsal penile artery; infiltration by a benign or malignant mass or an infectious agent; ventral curvature from any cause; presence of an active sexually transmitted disease; known active hepatitis B or C; known immune deficiency disease (including HIV), failure to achieve a sufficient erection (after prostaglandin E or Trimix administration), in the opinion of the investigator, to accurately measure the penile deformity, calcified plaque as evident by appropriate radiographic evaluation, penile X-ray, or penile ultrasound (noncontiguous stippling was allowed) that would prevent proper injection of study medication, + isolated hourglass deformity of the penis without curvature, plaque causing curvature of the penis located proximal to the base of the penis (injection of the local anesthetic would interfere with the injection of collagenase *Clostridium histolyticum* into the plaque), treatment or plans to undergo treatment for PD, including but not limited to any previous surgery, oral/topical agents within 3 months, injectional medical therapies within 3 months, extracorporeal shock wave therapy within 6 months, or use of mechanical devices within 2 weeks before the start of the study, use of or plans to use a mechanical device to induce a passive erection within 2 weeks before the start of the study, erectile dysfunction that was unresponsive to phosphodiesterase 5 inhibitors, compromised penile hemodynamics (determined by penile duplex Doppler ultrasound) found at screening that are determined by the investigator to be clinically significant, uncontrolled hypertension (determined by the investigator), known recent history of stroke, bleeding, or other significant medical condition, which in the investigator's opinion would make the participant unsuitable for enrollment, received an investigational drug or treatment (including collagenase *Clostridium histolyticum*) within 30 days before start of the study, allergy to collagenase or other medication required by the protocol, received anticoagulant medication (except for ≤ 165 mg aspirin daily or ≤ 800 mg of over-the-counter NSAIDs daily) during the 7 days before each dose of study drug, at any time, received collagenase *Clostridium histolyticum* for the treatment of PD **Total number of participants randomly assigned:** 836 **Group A** • Number of all participants randomly assigned: 555 • Age (years): 57.6 ± 8.5 • Disease duration (years): 4.1 ± 4.1 • Degrees penile curvature (degrees): 50.1 ± 14.4 • Number and size of plaques: NA **Group B** • Number of all participants randomly assigned: 281 • Age (years): 57.9 ± 8.3 • Disease duration (years): 4.1 ± 4.8 • Degrees penile curvature (degrees): 49.3 ± 14.0 • Number and size of plaques: NA
Interventions	**Group A:** collagenase *Clostridium histolyticum* 2 injections (interval of 24 to 72 hours between the injections) followed by 4 treatment cycles (6-week intervals) with 0.58 mg **Group B:** placebo (10 mM tris and 60 mM sucrose) with same schedule of Group A **Intervention duration:** 24 weeks **Follow-up (including intervention duration):** 52 weeks

Gelbard 2013 *(Continued)*

	Run-in period: none
Outcomes	**Primary outcome** • Percent improvement from baseline in penile curvature • Change from baseline in the PD symptom bother domain How measured: distance from the corona to the maximum point of curvature after injecting prostaglandin E1 or trimix into a corpus cavernosum to induce erection/PD questionnaire Time points measured: at baseline and 52 weeks Time points reported: at baseline and 52 weeks **Secondary outcome** • Proportion of treatment responders • Decrease in the severity of PD psychological and physical symptoms • Change in the IIEF overall satisfaction domain • Percent of composite responders • Change in penile plaque consistency • Penile length • Penile pain How measured: global assessment of PD questionnaire (defined as a participant with a global score of at least 1 (improved in a small but important way)/PD questionnaire/IIEF questionnaire/defined with 20.0% or greater improvement in penile curvature plus an improvement in the PDQ PD bother score of 1 or greater, or a change from reporting no sexual activity at screening to reporting sexual activity/NR/NR/PD questionnaire (pain score of 4 or greater at baseline screening) Time points measured: NR Time points reported: at baseline and 52 weeks **Safety outcome:** incidence of treatment-related adverse events and the change from baseline in laboratory values and vital signs How measured: NR Time points measured: at all study visits Time points reported: cumulative incidence **Subgroup:** none
Funding sources	Auxilium Pharmaceuticals
Declarations of interest	Auxilium, Biospecifics Technologies, American Medical Systems, Coloplast, Cook, Endo, Johnson & Johnson, Lilly, Medtronic, NIH, Slate, Theralogix, and VIVUS
Notes	**Protocol:** NCT01221597, NCT01221623 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Men were stratified by the degree of the penile curvature abnormality (30 to 60 or 61 to 90 degrees) and randomized to the CCh or placebo group 2:1 in favor of CCh". Judgment: randomization method was not described

Gelbard 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blinded placebo controlled study" Judgment: placebo-controlled study/participants and personnel were likely blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Low risk	Quote: "Double blinded placebo controlled study" Judgment: placebo-controlled study/outcome assessor was likely blinded
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Quality of life	High risk	Judgment: 401/555 (72.2%) and 211/281 (75.0%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Low risk	Judgment: 551/555 (99.2%) and 281/281 (100%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Degree of penile curvature	High risk	Judgment: 401/555 (72.2%) and 211/281 (75.0%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	High risk	Judgment: 401/555 (72.2%) and 211/281 (75.0%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Improvement in penile pain	High risk	Judgment: 401/555 (72.2%) and 211/281 (75.0%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Selective reporting (reporting bias)	Low risk	Protocol was published and the prespecified outcomes were described
Other bias	Low risk	Judgment: not detected

Hatzichristodoulou 2013

Study characteristics

Hatzichristodoulou 2013 *(Continued)*

Methods	**Study design:** placebo-controlled, prospective, randomized, single-blind study **Setting/country:** likely outpatient/single center/Germany **Dates when study was conducted:** July 2002 to May 2004
Participants	**Inclusion criteria:** men with previous unsuccessful oral medical therapy, age ≥ 18 years, and plaques and/or pain at erection and/or deviation, disease duration ≥ 12 months and additionally unchanged symptoms (deviation, pain, and plaques) for ≥ 3 months **Exclusion criteria:** men with prior penile surgery and erectile dysfunction not responding to phosphodiesterase-type-5 inhibitors or intracavernous injections **Total number of participants randomly assigned:** 102 **Group A** • Number of all participants randomly assigned: 51 • Age (years, range): 53.8 (25 to 72) • Disease duration: NA • Degrees penile curvature (degrees): 44 • Number and size of plaques: NA **Group B** • Number of all participants randomly assigned: 51 • Age (years, range): 55.2 (30 to 72) • Disease duration: NA • Degrees penile curvature (degrees): 43 • Number and size of plaques: NA
Interventions	**Group A:** Piezoson 100 lithotripter (Richard Wolf, Knittlingen, Germany) 6 times at weekly intervals, comprising 2000 shock waves per session with constant energy flow density of 0.29 mJ/mm^2 and emission frequency of 3 Hz **Group B:** interposition of a plastic membrane in the transducer, 6 times at weekly intervals with a same manner of group A **Intervention duration:** 6 weeks **Follow-up (including intervention duration):** 10 to 32 weeks **Run-in period:** none
Outcomes	• Plaque localization • Plaque size • Penile pain • Penile deviation • Sexual function How measured: palpation and sonography using a 7.5 MHz linear transducer/length and width in mm^2, was measured with a ruler/VAS ranging from 0 (no pain) to 10 (strong pain)/goniometer after artificial erection using Alprostadil (Viridal®, Schwarz Pharma, Monheim, Germany)/self-made scale regarding the ability to perform sexual intercourse (“impossible,” “hindered,” and “possible without restrictions”) Time points measured: at baseline and follow-up examination (no definition of follow-up period in method) Time points reported: at baseline and follow-up (median of 4 weeks (range 4 to 26 weeks)

Hatzichristodoulou 2013 *(Continued)*

	Safety outcome: complication How measured: NR Time points measured: NR Time points reported: NR **Subgroup:** none
Funding sources	NR
Declarations of interest	None
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computer-generated sequence"
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single blinded: participants"
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	High risk	Quote: "Single blinded: participants"
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Patient-reported ability to have intercourse	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Degree of penile curvature	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias)	Low risk	Judgment: all participants were included in the analysis

Hatzichristodoulou 2013 *(Continued)*

Discontinuation from treatment		
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	Low risk	Judgment: 50/51 (98.0%) and 49/51 (96.0%) of randomized participants in the experimental and control groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Improvement in penile pain	Low risk	Judgment: all participants were included in the analysis
Selective reporting (reporting bias)	Unclear risk	Judgment: protocol was not available, and the complication outcome was not prespecified
Other bias	Low risk	Judgment: not detected

Hellstrom 2006

Study characteristics	
Methods	**Study design:** single-blind, placebo-controlled, parallel study **Setting/country:** likely outpatient/8 centers/USA **Dates when study was conducted:** June 2000 to February 2003
Participants	**Inclusion criteria:** men aged 18 years or older with a history of PD of 12 months or more and a single plaque, and at least 30-degree penile curvature on erection **Exclusion criteria:** men with PD who had calcified plaque **Total number of participants randomly assigned:** 117 **Group A** • Number of all participants randomly assigned: 55 • Age (years): 55.8 • Disease duration: NR* • Degrees penile curvature (degrees): 49.9 ± 2.4 • Number and size of plaques (cm^2): 4.8 ± 0.95 **Group B** • Number of all participants randomly assigned: 62 • Age (years): 54.3 • Disease duration: NR* • Degrees penile curvature (degrees): 50.9 ± 2.5 • Number and size of plaques (cm^2): 4.5 ± 0.55 *Overall disease duration (years): 1.7
Interventions	**Group A:** 5 * 106 U interferon alpha-2b in 10 mL saline injections every other week for a total of 6 injections **Group B:** 10 mL saline injections every other week for a total of 6 injections

Hellstrom 2006 *(Continued)*

	Intervention duration: 12 weeks **Follow-up (including intervention duration):** 16 weeks **Run-in period:** none
Outcomes	• Patient erectile function • Cavernous blood flow parameters • Plaque size • Penile curvature • Plaque density How measured: modified erectile function domain of the IIEF questionnaire/penile Doppler ultrasound/handheld calipers/protractor in the erect state/questionnaire of each patient and graded as between 0 and 3 Time points measured: before and after treatment Time points reported: before and after treatment **Safety outcome:** adverse event How measured: NR Time points measured: NR Time points reported: likely cumulative incidence **Subgroup:** none
Funding sources	NR
Declarations of interest	Vivus, Mentor, Lilly ICOS, Bayer, Pfizer, Johnson and Johnson, Unimed, Watson, Macrochem, Auxilium, and Sanofi-Synthelabo
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgment: not described
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single blinded placebo controlled study" Judgment: personnel were not likely blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	High risk	Quote: "Single blinded placebo controlled study" Judgment: outcome assessor was not likely blinded
Blinding of outcome assessment (detection bias)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding

Hellstrom 2006 *(Continued)*

Objective outcome (discontinuation)		
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Unclear risk	Judgment: 50/55 (90.9%) and 53/62 (85.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Degree of penile curvature	Unclear risk	Judgment: 50/55 (90.9%) and 53/62 (85.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Improvement in penile pain	Unclear risk	Judgment: 50/55 (90.9%) and 53/62 (85.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Selective reporting (reporting bias)	Unclear risk	Judgment: protocol was not available, and the adverse event outcome was not prespecified
Other bias	Low risk	Judgment: not detected

Moncada 2019

Study characteristics	
Methods	**Study design:** parallel, placebo-controlled randomized controlled trial **Setting/country:** 6 centers, Spain, India, Germany, USA **Dates when study was conducted:** March 2016 and June 2017
Participants	**Inclusion criteria:** patients diagnosed with PD for at least 1 year, without ED, no significant pain and with a unidirectional curvature of at least 45°, stable for at least 3 months prior to inclusion into the study. **Exclusion criteria:** patients with hourglass deformity, complex curvatures or areas of tunical indentation, patients submitted to previous collagenase or any other injectional treatments were also excluded. **Total number of participants randomly assigned:** 93 **Group A:** • Number of participants randomly assigned: 47 • Age (years): 57.9 ± 11.69 • Disease duration (years): 19 months ± 6.3 • Degree of penile curvature (degrees): 72.3 (61 to 105) • Number and size of plaques: 1 **Group B:** • Number of participants randomly assigned: 46

Moncada 2019 *(Continued)*

- Age (years): 58.2 ± 11.57
- Disease duration (years): 20 ± 4.7
- Degree of penile curvature (degrees): 68.7 (58 to 102)
- Number and size of plaques: 1

Interventions	**Group A:** Penismaster PRO traction device 3 to 8 hours per day **Group B:** no intervention **Intervention duration:** 12 weeks **Follow-up (including intervention duration):** 12 weeks **Run-in period:** NA
Outcomes	**Primary outcome** • Change in the degree of curvature How measured: goniometer degree of curvature measured in the fully erect state after intracavernosal injection of alprostadil at baseline Time points measured: baseline, 1, 2, and 3 months Time points reported: baseline, 1, 2, and 3 months **Secondary outcome** • Stretched penile length • Peyronie's Disease Questionnaire (PDQ) scores • Erectile function • Adverse events How measured: Spanish version of the PD Questionnaire who experienced both a ≥ 20.0% improvement in penile curvature deformity and either an improvement in PDQ PD symptom bother domain score of ≥ 1 or a change from no sexual activity at screening to reporting sexual activity, IIEF-EF Time points measured: baseline, 1, 2, and 3 months Time points reported: baseline, 1, 2, and 3 months
Funding sources	None
Declarations of interest	None
Notes	**Protocol:** none found **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgment: not described
Allocation concealment (selection bias)	Unclear risk	Judgment: not described

Moncada 2019 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Judgment: not described
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Low risk	Quote: "Patients were assessed by an independent examiner in every centre who was blind to the assignment group of the patient"
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Degree of penile curvature	Unclear risk	Judgment: 41/47 (87.2%) and 39/46 (84.8%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Improvement in penile pain	Unclear risk	Judgment: 41/47 (87.2%) and 39/46 (84.8%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Selective reporting (reporting bias)	Unclear risk	Judgment: while the review outcomes were prespecified in the methods, a protocol was not available
Other bias	Low risk	Judgment: not detected

Mortensen 2021

Study characteristics	
Methods	**Study design:** randomized, single-blind, placebo-controlled clinical trial **Setting/country**: outpatient/single center/Denmark **Dates when study was conducted:** May 2018 to February 2020
Participants	**Inclusion criteria:** patients diagnosed with PD > 6 mo and in stable phase (defined as no penile curvature change within the last 3 months or disease duration > 12 months), penile curvature 20 to 90 degrees, age 18 to 80 years, able to speak and understand Dutch and provide written informed consent **Exclusion criteria:** previous penile surgery, previous ESWT treatment **Total number of participants randomly assigned:** 32 **Group A** • Number of all participants randomly assigned: 14 • Age (years): 61.7 ± 8.3 • Disease duration (months): 16.21 ± 14.1

Mortensen 2021 *(Continued)*

- Curvature (degrees): 45 ± 16.74
- Number and size of plaques: NR

Group B

- Number of all participants randomly assigned: 16
- Age (years): 63 ± 7.35
- Disease duration (months): 18.38 ± 16.93
- Curvature (degrees): 47.6 ± 12.6
- Number and size of plaques: NR

Interventions	**Group A:** high-energy level shock wave therapy (Storz Duolith ESWT system, Storz Medical AG, Switzerland): treatment session (2000 SWs delivered at 0.15mJ/mm^2 to 0.15mJ/mm^2 at 3 Hz depending on the patients pain threshold) per week for 5 weeks **Group B:** sham therapy: same settings and setup, completely shock wave absorbant stand-off used **Intervention duration:** 6 months **Follow-up (including intervention duration):** 1 month, 3 months, and 6 months **Run-in period:** none
Outcomes	• Penile curvature • Erectile function • Penile pain • Adverse effects How measured: IIEF-5/PDQ/VAS/image Time points measured: at baseline, 1 month, 3 months, and 6 months Time points reported: at baseline, 1 month, 3 months, and 6 months
Funding sources	None
Declarations of interest	None
Notes	**Protocol:** NCT035305440 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Judgment: computer-generated randomization sequence used
Allocation concealment (selection bias)	Low risk	Judgment: allocation was performed externally by an independent employee after participant enrollment; allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Judgment: participants were blinded for up to 6 months using shock wave-absorbant "sham pads". Also, "group allocation was concealed" during follow-up; both parties likely blinded.
Blinding of outcome assessment (detection bias)	Low risk	Judgment: patients reported to be blinded as well as investigators measuring curvature

Mortensen 2021 *(Continued)*

Subjective outcomes (all except discontinuation)		
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: blinding not relevant
Incomplete outcome data (attrition bias) Quality of life	Unclear risk	Judgment: of those randomized, 14/16 participants in the treatment group and 16/16 in the control group included in the analysis
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Unclear risk	Judgment: 14/16 participants in the treatment group and 16/16 in the control group included in the analysis
Incomplete outcome data (attrition bias) Degree of penile curvature	Unclear risk	Judgment: 13 of 16 participants (81%) in the treatment group and 14 of 16 (88%) participants in the control group included in the 6-month analysis
Incomplete outcome data (attrition bias) Discontinuation from treatment	Unclear risk	Judgment: 14/16 participants in the treatment group and 16/16 in the control group included in the 6-month analysis
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	Unclear risk	Judgment: 14/16 participants in the treatment group and 16/16 participants in the control group included in the 6-month analysis
Incomplete outcome data (attrition bias) Improvement in penile pain	Unclear risk	Judgment: 14/16 participants in the treatment group and 16/16 participants in the control group included in the 6-month analysis
Selective reporting (reporting bias)	Low risk	Judgment: a protocol was published, and the prespecified outcomes were analyzed and reported as intended
Other bias	Low risk	No other sources of bias identified

Palmieri 2009

Study characteristics	
Methods	**Study design:** prospective, randomized, double-blind, placebo-controlled clinical trial **Setting/country:** likely outpatient/single center/Italy **Dates when study was conducted:** May 2007 to September 2008
Participants	**Inclusion criteria:** men aged between 18 and 75 years with PD not > 12 months, only one plaque demonstrated by basal and dynamic sonography and by palpation with a maximum size of 3.75 cm^2, no previous medical or surgical therapies for PD, stable sexual relationship, presence of painful erections (score ≥ 5 on a VAS with a score ranging from 0 to 10), erectile dysfunction, and penis recurvatum (the last 3 criteria could be present as singular features or could be variously associated)

Palmieri 2009 *(Continued)*

	Exclusion criteria: men with blood coagulation disorders, cardiac pacemaker, lower urinary tract infections, and vascular disorders in the path of the shock waves **Total number of participants randomly assigned:** 100 **Group A** • Number of all participants randomly assigned: 50 • Age (years, range): 54 (24 to 76) • Disease duration (months, range): 8.74 (5 to 12) • Degrees penile curvature (degrees, range): 28.88 (15 to 40) • Number and size of plaques (cm^2, range): 1.53 (0.25 to 3.50) **Group B** • Number of all participants randomly assigned: 50 • Age (years, range): 55.2 (30 to 70) • Disease duration (months, range): 8.62 (5 to 12) • Degrees penile curvature (degrees, range): 29.45 (15 to 45) • Number and size of plaques (cm^2, range): 1.41 (0.49 to 3.75)
Interventions	**Group A:** 2000 impulses at each ESWT (Storz Duolith ESWT system, Storz Medical AG, Switzerland) session with an energy flux density of 0.25 mJ/mm^2 and an emission frequency of 4 Hz once weekly **Group B:** same manner with group A using modified nonfunctioning transducer **Intervention duration:** 4 weeks **Follow-up (including intervention duration):** 16 and 28 weeks **Run-in period:** none
Outcomes	• Presence and severity of painful erections • Erectile function • Quality of life • Penile plaque size • Penile curvature • Treatment preference How measured: VAS score/IIEF – 5/structured interview/Doppler ultrasonography/goniometer on pictures during full erection/participants' responses (yes, no, or don't know to the following question: "Would you recommend this treatment to a friend?") Time points measured: at baseline, 12, and 24 weeks after final intervention session Time points reported: at baseline, 12, and 24 weeks after final intervention session **Safety outcome:** adverse event How measured: NR Time points measured: NR Time points reported: likely cumulative incidence **Subgroup:** none
Funding sources	None
Declarations of interest	None

Palmieri 2009 *(Continued)*

Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgment: not described
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blinded placebo controlled study" Judgment: placebo-controlled study/participants and personnel were likely blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Low risk	Quote: "Double blinded placebo controlled study" Judgment: placebo-controlled study/outcome assessor was likely blinded
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Quality of life	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Degree of penile curvature	Unclear risk	Judgment: 44/50 (88.0%) and 44/50 (88.0%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	Unclear risk	Judgment: no information (not measured)
Incomplete outcome data (attrition bias) Improvement in penile pain	Unclear risk	Judgment: 42/50 (84.0%) and 43/50 (86.0%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively

Palmieri 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Judgment: no protocol was available
Other bias	Low risk	Judgment: not detected

Rehman 1998

Study characteristics	
Methods	**Study design:** randomized, single-blind, placebo-controlled study **Setting/country:** likely outpatient/single-center/USA **Dates when study was conducted:** 1994 to 1996
Participants	**Inclusion criteria:** men with (1) age range 35 to 70 years with clinical evidence of PD, that is, pain and plaque along with deformity of the penis of at least 1-year duration; (2) discontinuation of any previous oral or other medication for PD for at least 3 months **Exclusion criteria:** men with any history of calcium channel blocker therapy or therapy interfering with calcium channel blockers **Total number of participants randomly assigned:** 18 **Group A** • Number of all participants randomly assigned: NR • Age (years): NR* • Disease duration: NR** • Degrees penile curvature (degrees): 37.71 ± 9.3 • Number and size of plaques (cm): 3.1 ± 0.51 **Group B** • Number of all participants randomly assigned: NR • Age (years): NR* • Disease duration: NR** • Degrees penile curvature (degrees): 33.57 ± 9.7 • Number and size of plaques (cm): 2.9 ± 0.55 *Overall age (years, range): 52 (37 to 67) **Overall disease duration (months, range): 16 (11 to 24)
Interventions	**Group A:** injections of verapamil 10 to 27 mg/with a 10 mL syringe and a 25 gauge needle once a week **Group B:** injections of saline with a 10 mL syringe a 25 gauge needle once a week **Intervention duration:** 6 months **Follow-up (including intervention duration):** 9 months **Run-in period:** none
Outcomes	• Plaque size and volume • Penile curvature • Quality of erection

Rehman 1998 *(Continued)*

	How measured: calipers (Vmoeleov OP-270, Germany) and duplex ultrasound/NR/self-administered questionnaire Time points measured: at baseline and 3 months after the treatment Time points reported: at baseline and 3 months after the treatment **Safety outcome** • Blood pressure and heart rate • Adverse event How measured: NR/NR Time points measured: at time of injection for first 3 months/NR Time points reported: at time of injection for first 3 months/likely cumulative incidence **Subgroup:** none
Funding sources	NR
Declarations of interest	NR
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgment: not described
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single blinded placebo controlled study" Judgment: personnel were not likely blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	High risk	Quote: "Single blinded placebo controlled study" Judgment: outcome assessor was not likely blinded
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Patient-reported ability to have intercourse	High risk	Judgment: 14/18 (77.7%) were included in the analysis
Incomplete outcome data (attrition bias)	High risk	Judgment: 14/18 (77.7%) of randomized participants were included in the analysis

Rehman 1998 *(Continued)*

Treatment-related adverse effects		
Incomplete outcome data (attrition bias) Degree of penile curvature	High risk	Judgment: 14/18 (77.7%) of randomized participants were included in the analysis
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	High risk	Judgment: 14/18 (77.7%) of randomized participants were included in the analysis
Selective reporting (reporting bias)	High risk	Judgment: protocol was not available and penile curvature outcome was reported without any description in method
Other bias	Low risk	Judgment: not detected

Soh 2010

Study characteristics	
Methods	**Study design:** randomized, single-blind, placebo-controlled study **Setting/country:** likely outpatient/Japan **Dates when study was conducted:** April 2005 to May 2008
Participants	**Inclusion criteria:** men with: (i) duration of disease more than 12 months, and meeting the criteria for PD in the transition period of acute and chronic phase; (ii) any drugs that might affect the course of PD should be discontinued 6 months before enrollment; (iii) plaque total area less than 2 cm^2 without calcification **Exclusion criteria:** men with: (i) calcified plaques; (ii) ventral curvatures; (iii) congenital penile curvature or chordee with hypospadias **Total number of participants randomly assigned:** 74 **Group A** • Number of all participants randomly assigned: 37 • Age (years): 52.4 ± 10.9 • Disease duration (months): 18.1 ± 9.5 • Degrees penile curvature (degrees): 30.9 • Number and size of plaques (cm^3): 1.48 **Group B** • Number of all participants randomly assigned: 37 • Age (years): 52.1 ± 10.5

Soh 2010 *(Continued)*

- Disease duration (months): 18.3 ± 9.4
- Degrees penile curvature (degrees): 32.1
- Number and size of plaques (cm^3): 1.48

Interventions	**Group A:** 10 mg nicardipine (10 mg diluted in 10 mL of distilled water) injections biweekly **Group B:** 10 mL of normal saline biweekly **Intervention duration:** 10 weeks **Follow-up (including intervention duration):** 48 weeks **Run-in period:** none
Outcomes	• Penile pain • Erectile function • Plaque size • Penile curvature How measured: international pain scale (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain)/IIEF-5/ultrasonography at maximum rigidity after 20 mg intracavernosal injection of alprostadil/photograph at maximum rigidity after 20 mg intracavernosal injection of alprostadil Time points measured: at baseline, 2, 4, 8, 12, 24, and 48 weeks (penile pain and erectile function)/before therapy and 48 weeks after initiation of the therapy (penile size and curvature) Time points reported: at baseline, 2, 4, 8, 12, 24, and 48 weeks (penile pain and erectile function)/before therapy and 48 weeks after initiation of the therapy (penile size and curvature) **Safety outcome:** adverse event How measured: Common Terminology Criteria for Adverse Events Time points measured: each patient's visit to clinic Time points reported: likely cumulative incidence **Subgroup:** none
Funding sources	NR
Declarations of interest	None
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized the patients according to a computer-generated random table in two groups"
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Patients were blinded to the group to which they belonged" Judgment: participants were blinded, personnel was not blinded

Soh 2010 *(Continued)*

Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	High risk	Quote: "Patients were blinded to the group to which they belonged" Judgment: outcome assessor was not blinded
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Unclear risk	Judgment: 32/37 (86.4%) and 30/37 (81.0%) of randomized participants in the experimental and control groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Degree of penile curvature	Unclear risk	Judgment: 32/37 (86.4%) and 30/37 (81.0%) of randomized participants in the experimental and control groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Improvement in penile pain	Unclear risk	Judgment: 32/37 (86.4%) and 30/37 (81.0%) of randomized participants in the experimental and control groups were included in the analysis, respectively
Selective reporting (reporting bias)	Unclear risk	Judgment: while the review outcomes were prespecified in the methods, a protocol was not available
Other bias	Low risk	Judgment: not detected

Weidner 2005

Study characteristics	
Methods	**Study design:** placebo-controlled, double-blinded, randomized study **Setting/country:** likely outpatient/multi-center (11 centers)/Germany **Dates when study was conducted:** NR
Participants	**Inclusion criteria:** men with a history of a maximum of 12 months, no prior treatment, and no evidence of calcified plaques **Exclusion criteria:** men with a history of prior treatment, symptoms of more than 12 months duration, sonographic evidence of calcification, and/or no response to the intracavernous injection test were excluded. Further clinical exclusion criteria included evidence of diabetes mellitus, compensated nephropathy, and chronic gastric and bowel diseases. **Total number of participants randomly assigned:** 103 **Group A** • Number of all participants randomly assigned: 51 • Age (years, range): 49 (18 to 70)

Weidner 2005 *(Continued)*

- Disease duration (months, range): 6 (1 to 12)
- Degrees penile curvature (degrees): NR
- Number and size of plaques (mm^2): 264.1 ± 36.6 (standard error)

Group B

- Number of all participants randomly assigned: 52
- Age (years): 53 (range 24 to 71)
- Disease duration (median, range): 6 months (1 to 12)
- Degrees penile curvature (degrees): NR
- Number and size of plaques (mm^2): 259.8 mm^2 ± 28.8 (standard error)

Interventions	**Group A:** potassium para-aminobenzoate 3 g powder 4 times daily **Group B:** probably same regimen of placebo **Intervention duration:** 12 months **Follow-up (including intervention duration):** 12 months (6 months after end of treatment) **Run-in period:** none
Outcomes	• Response • Penile pain • Erectile function How measured: full resolution or as reduction in plaque size (product of length and with in mm^2), and/or reduction in penile curvature of at least 30% in comparison to the initial evaluation/graduated pain score (grade 0 = no pain, grade 1 = mild, grade 2 = moderate, grade 3 = severe pain)/6 grading after intracavernous injection (E0 no response; E1 slight tumescence, no rigidity; E2 medium tumescence, no rigidity; E3 full tumescence, slight rigidity; E4 full tumescence, medium rigidity; E5 full erection) Time points measured: at baseline, 1, 2, 3, 6, 9, and 12 months Time points reported: at baseline and 12 months **Safety outcome:** adverse events How measured: NR Time points measured: NR Time points reported: likely cumulative incidence **Subgroup:** none
Funding sources	Glenwood GmbH
Declarations of interest	NR
Notes	**Protocol:** NA **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Judgment: not described

Weidner 2005 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "The placebo powder was a mixture of potassium citrate, lactose, hydrous, and potassium chloride identical in colour and appearence to the active drug" Judgment: placebo-controlled study/participants and personnel were likely blinded
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Low risk	Quote: "The placebo powder was a mixture of potassium citrate, lactose, hydrous, and potassium chloride identical in colour and appearence to the active drug" Judgment: placebo-controlled study/outcome assessor was likely blinded
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Patient-reported ability to have intercourse	High risk	Judgment: 35/51 (68.6%) and 40/52 (76.9%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Treatment-related adverse effects	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Degree of penile curvature	High risk	Judgment: 35/51 (68.6%) and 40/52 (76.9%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Discontinuation from treatment	Low risk	Judgment: all participants were included in the analysis
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	High risk	Judgment: 35/51 (68.6%) and 40/52 (76.9%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Improvement in penile pain	High risk	Judgment: 35/51 (68.6%) and 40/52 (76.9%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Selective reporting (reporting bias)	Unclear risk	Judgment: while the review outcomes were prespecified in the methods, a protocol was not available
Other bias	Low risk	Judgment: not detected

Ziegelmann 2019

Study characteristics	
Methods	**Study design:** randomized, controlled, single-blind trial **Setting/country:** single-center, USA **Dates when study was conducted:** October 2017 to August 2018
Participants	**Inclusion criteria:** Peyronie's disease, age greater than 18 years and more than 30 degrees of curvature **Exclusion criteria:** stretched penile length less than 7 cm and severe diabetes (end organ failure) **Total number of participants randomly assigned:** 110 **Group A:** • Number of participants randomly assigned: 82 • Age (years): 58.5 ± 7.0 • Disease duration (years): 46.0 ± 44.9 • Degree of penile curvature (degrees): 45.4 ± 13.4 • Number and size of plaques: NA **Group B:** • Number of participants randomly assigned: 28 • Age (years): 58.1 ± 9.7 • Disease duration (years): 51.8 ± 33.3 • Degree of penile curvature (degrees): 44.2 ± 12.0 • Number and size of plaques: NA **Subgroup:** various treatment durations of 30 to 90 minutes per day
Interventions	**Group A:** Restore X mechanical traction device for 30 min 1 to 3 times daily **Group B:** no therapy **Intervention duration:** 3 months **Follow-up (including intervention duration):** 3 months **Run-in period:** NA
Outcomes	**Primary outcome** • Adverse events How measured: questionnaire Time points measured: 3 months Time points reported: 3 months **Secondary outcome** • Change in penile curvature • Penile length • Erectile function change • Satisfaction, ability to penetrate • Reduction in need for surgery or further therapy • Satisfaction compared to other penile traction devices and Peyronie's disease therapies

Ziegelmann 2019 *(Continued)*

	How measured: ruler, protractor, IIEF, and Peyronie's Disease Questionnaires Time points measured: 3 months Time points reported: 3 months
Funding sources	**Funding sources:** PathRight Medical
Declarations of interest	**Declarations of interest:** PathRight Medical
Notes	**Protocol:** ClinicalTrials.gov NCT03389854 **Language of publication:** English

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization tables were created a priori based on primary curvature direction and 30 to 60 vs greater than 60 degrees"
Allocation concealment (selection bias)	Unclear risk	Judgment: not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Single-blind" Judgment: investigator and outcomes assessor were blinded (in protocol)
Blinding of outcome assessment (detection bias) Subjective outcomes (all except discontinuation)	Low risk	Quote: "Single-blind" Judgment: investigator and outcomes assessor were blinded
Blinding of outcome assessment (detection bias) Objective outcome (discontinuation)	Low risk	Judgment: objective outcomes are unlikely affected by lack of blinding
Incomplete outcome data (attrition bias) Patient-reported ability to have intercourse	High risk	Judgment: 63/82 (76.8%) and 27/28 (96.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Quality of life	High risk	Judgment: 63/82 (76.8%) and 27/28 (96.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Treatment-related adverse effects	High risk	Judgment: 63/82 (76.8%) and 27/28 (96.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Degree of penile curvature	Unclear risk	Judgment: 62/82 (76.8%) and 27/28 (96.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias)	Unclear risk	Judgment: 63/82 (76.8%) and 27/28 (96.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively

Ziegelmann 2019 *(Continued)*

Discontinuation from treatment		
Incomplete outcome data (attrition bias) Subjective patient-reported change in penile curvature	Unclear risk	Judgment: 63/82 (76.8%) and 27/28 (96.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Incomplete outcome data (attrition bias) Improvement in penile pain	Unclear risk	Judgment: 63/82 (76.8%) and 27/28 (96.4%) of randomized participants in the experimental and placebo groups were included in the analysis, respectively
Selective reporting (reporting bias)	Low risk	Protocol was published, and the prespecified outcomes were described
Other bias	Low risk	Judgment: none detected

ED: erectile dysfunction; ESWT: extracorporeal shock wave therapy; IIEF: International Index of Erectile Function; NA: not available; NR: not reported; NSAIDs: non-steroidal anti-inflammatory drugs; PD: Peyronie's disease; PDQ: Peyronie's Disease Questionnaire; RCT: randomized controlled trial; SEP: Sexual Encounter Profile; VAS: visual analog scale

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alizadeh 2014	Wrong comparator
Amicuzi 2020	Wrong study population
Biagiotti 2001	Wrong comparator
Cai 2020	Wrong comparator
Candebat Montero 2008	Wrong comparator
Carson 2015	Wrong comparator
Cavallini 2002	Wrong comparator
Cavallini 2007	Wrong comparator
Dang 2004	Wrong study design (non-randomized controlled trial)
Dell'Atti 2015	Wrong comparator
Di Stasi 2004	Wrong comparator
Favilla 2014	Wrong comparator
Felipetto 1995	Wrong comparator
Fitch 2007	Wrong comparator
Gelbard 1993	Wrong intervention (one injection of collagenase at baseline)

Study	Reason for exclusion
Gennaro 2015	Wrong study design (non-randomized controlled trial)
Glina 2007	Commentary
Goldstein 2020	Wrong study design (phase IV extension)
Greenfield 2007	Wrong comparator
Heidari 2010	Wrong study design (non-randomized controlled trial)
Inal 2006	Wrong comparator
Joseph 2020	Wrong study design (open-label, non-randomized follow-up)
Levine 2015	Wrong study design (phase 3, open-label study)
Lipshultz 2015	Duplicate
Mehrsai 2013	Wrong comparator
Mirone 1999	Wrong comparator
Mirone 2000	Wrong study design (non-randomized controlled trial)
Montorsi 2000	Wrong comparator
Ozturk 2014	Wrong comparator
Palmieri 2012	Wrong comparator
Paulis 2013	Wrong study design (non-randomized controlled trial)
Pavone 2017	Wrong comparator
Prieto Castro 2003	Wrong comparator
Riedl 2005	Wrong comparator
Safarinejad 2004	Authenticity concerns
Safarinejad 2007	Authenticity concerns
Safarinejad 2009	Authenticity concerns
Safarinejad 2010a	Authenticity concerns
Safarinejad 2010b	Authenticity concerns
Seftel 2016	Commentary
Sempels 2015	Wrong comparator
Shirazi 2009	Authenticity concerns
Teloken 1999	Wrong comparator

Study	Reason for exclusion
Toscano 2016	Wrong comparator
Twidwell 2016	Wrong comparator
Watkin 2015	Commentary

Characteristics of ongoing studies *[ordered by study ID]*

Allameh 2018

Study name	Assessment of treatment efficacy of Nd-YAG laser beside intra lesion verapamil injection in Peyronie's disease patients referring to Shohada-e-Tajrish hospital: a randomized clinical trial
Methods	**Study design:** single-blinded, parallel randomized controlled trial **Setting/country:** Iran **Dates when study was conducted:** September 2017 **Sponsor:** Shahid Beheshti University of Medical Sciences
Participants	**Inclusion criteria:** all patients with Peyronie's disease; aged 18 years and over; have Peyronie's disease for at least for 6 months **Exclusion criteria:** patients with Peyronie's disease who have received multiple treatments; skin disorder in the penis; history of inflammatory diseases of the skin; uncontrolled hypertension; history of heart attacks in the last 1 month; patients with acute phase or released fibrosis plaque of the penis; patients who are not satisfied to enter the study; 18 years old or older **Total number of participants randomly assigned:** 80
Interventions	**Group A:** 6 weeks, 2 sessions in a week, 1064 laser with a power of 0.5 watts and a dose of 50 joules per square centimeter in an area of 1 centimeter square with a time of 1 minute and 40 seconds per session with a BTL-6000 high-intensity LASER 12W, and 10 mm probe, and 6 injections of verapamil intra-lesion with insulin needle will be performed weekly **Group B:** control group: only the standard treatment of verapamil injection is done, and the laser probe is placed on the plaque with a red light only **Intervention duration:** 6 weeks **Follow-up (including intervention duration):** 3 months **Run-in period:** NA
Outcomes	**Primary outcome:** plaque size 1 and 3 months after end of treatment **Secondary outcome:** NA
Starting date	September 2017
Contact information	Name of recruitment center: Laser Application Research Center in Medical Sciences Full name of responsible person: Dr. Farzad Allameh Street address: Shohadaye Tajrish Hospital, Tajrish, Tehran City: Tehran

Allameh 2018 *(Continued)*

	Phone: +98 21 2274 9221 Email: laser.cntr@yahoo.com
Notes	Protocol: IRCT201710088146N27 https://www.irct.ir/trial/8585

Lund 2018

Study name	Low-intensity extracorporeal shockwave therapy and vacuum erectile device as a treatment for Peyronie's disease
Methods	**Study design:** prospective, randomized, double-blinded, placebo-controlled trial with follow-up after 1, 3, and 6 months **Setting/country:** single-center, Denmark **Dates when study was conducted:** May 2018 to present
Participants	**Inclusion criteria:** Peyronie's disease (PD) for more than 6 months, penile curve greater than 30 degrees and less than 90 degrees, age 18 to 80, no previous penile surgery, informed consent, able to speak and understand Danish **Exclusion criteria:** penile curve greater than 90 degrees, previous surgery for PD, patients undergoing other interventions for PD **Total number of participants randomly assigned:** 50
Interventions	**Group A:** low-intensity extracorporeal shockwave therapy + penile pump **Group B:** placebo shock waves + penile pump **Intervention duration:** NA **Follow-up (including intervention duration):** follow-up at 1, 3, and 6 months **Run-in period:** NA
Outcomes	Primary outcome: change in penile curvature from baseline to follow-up at 1, 3, and 6 months. Penile curvature is measured based on pictures submitted by the patient. Secondary outcome: change in penile pain, change in erectile function, change in Peyronie's disease questionnaire score to evaluate psychological/physical consequences of Peyronie's disease
Starting date	March 2018
Contact information	Lars Lund MD, Odense University Hospital Lars.Lund@rsyd.dk
Notes	**Protocol:** NCT03530540

NA: not available

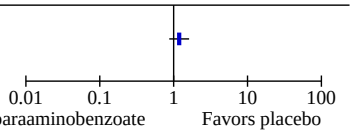
DATA AND ANALYSES

Comparison 1. Oral potassium paraaminobenzoate versus placebo (short-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Patient-reported ability to have intercourse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.2 Treatment-related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.3 Discontinuation from treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.4 Subjective patient-reported change in penile curvature	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

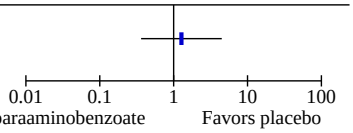
Analysis 1.1. Comparison 1: Oral potassium paraaminobenzoate versus placebo (short-term), Outcome 1: Patient-reported ability to have intercourse

Study or Subgroup	Potassium paraaminobenzoate Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Weidner 2005	26	35	25	40	1.19 [0.87 , 1.62]	



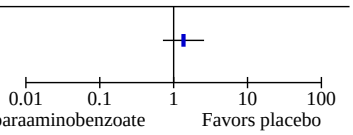
Analysis 1.2. Comparison 1: Oral potassium paraaminobenzoate versus placebo (short-term), Outcome 2: Treatment-related adverse effects

Study or Subgroup	Potassium paraaminobenzoate Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Weidner 2005	5	51	4	52	1.27 [0.36 , 4.48]	



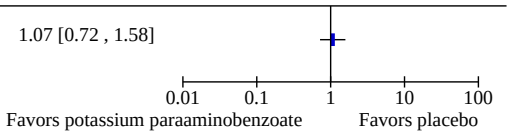
Analysis 1.3. Comparison 1: Oral potassium paraaminobenzoate versus placebo (short-term), Outcome 3: Discontinuation from treatment

Study or Subgroup	Potassium paraaminobenzoate Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Weidner 2005	16	51	12	52	1.36 [0.72 , 2.58]	



Analysis 1.4. Comparison 1: Oral potassium paraaminobenzoate versus placebo (short-term), Outcome 4: Subjective patient-reported change in penile curvature

Study or Subgroup	Potassium paraaminobenzoate Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Weidner 2005	19	30	19	32	1.07 [0.72 , 1.58]

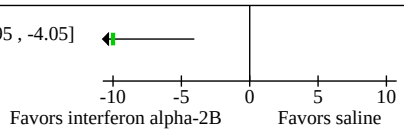


Comparison 2. Intralesional interferon alpha-2B versus saline (short-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Degree of penile curvature	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2 Discontinuation from treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

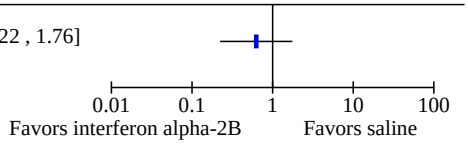
Analysis 2.1. Comparison 2: Intralesional interferon alpha-2B versus saline (short-term), Outcome 1: Degree of penile curvature

Study or Subgroup	Interferon alpha-2B Mean	SD	Total	Saline Mean	SD	Total	Mean Difference IV, Random, 95% CI
Hellstrom 2006	36.4	14.8	50	46.4	16	53	-10.00 [-15.95 , -4.05]



Analysis 2.2. Comparison 2: Intralesional interferon alpha-2B versus saline (short-term), Outcome 2: Discontinuation from treatment

Study or Subgroup	Interferon alpha-2B Events	Total	Saline Events	Total	Risk Ratio M-H, Random, 95% CI
Hellstrom 2006	5	55	9	62	0.63 [0.22 , 1.76]

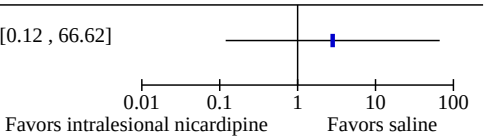


Comparison 3. Intralesional nicardipine versus saline (long-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Treatment-related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.2 Degree of penile curvature	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.3 Discontinuation from treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.4 Improvement in penile pain	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

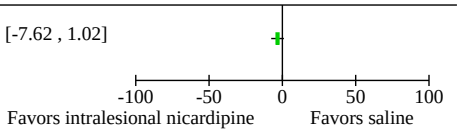
Analysis 3.1. Comparison 3: Intralesional nicardipine versus saline (long-term), Outcome 1: Treatment-related adverse effects

	Intralesional nicardipine		Saline		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Soh 2010	1	32	0	30	2.82 [0.12 , 66.62]	



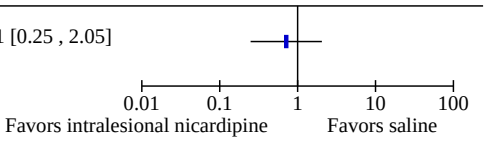
Analysis 3.2. Comparison 3: Intralesional nicardipine versus saline (long-term), Outcome 2: Degree of penile curvature

	Intralesional nicardipine			Saline			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Soh 2010	25.8	8.68	32	29.1	8.68	30	-3.30 [-7.62 , 1.02]	



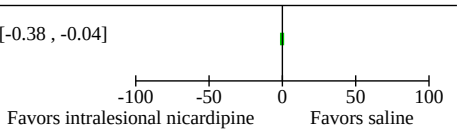
Analysis 3.3. Comparison 3: Intralesional nicardipine versus saline (long-term), Outcome 3: Discontinuation from treatment

	Intralesional nicardipine		Saline		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Soh 2010	5	37	7	37	0.71 [0.25 , 2.05]	



Analysis 3.4. Comparison 3: Intralesional nicardipine versus saline (long-term), Outcome 4: Improvement in penile pain

Study or Subgroup	Intralesional nicardipine Mean	SD	Total	Saline Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Soh 2010	0.54	0.34	32	0.75	0.34	30	-0.21 [-0.38 , -0.04]	

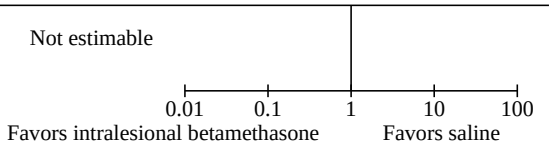


Comparison 4. Intralesional betamethasone versus saline (long-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Treatment-related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.2 Discontinuation from treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.3 Subjective patient-reported change in penile curvature	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

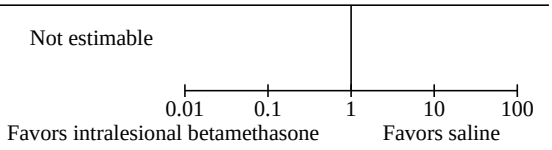
Analysis 4.1. Comparison 4: Intralesional betamethasone versus saline (long-term), Outcome 1: Treatment-related adverse effects

Study or Subgroup	Betamethasone Events	Total	Saline Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cipollone 1998	0	15	0	15	Not estimable	



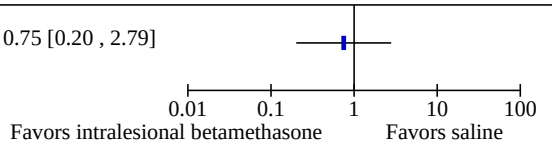
Analysis 4.2. Comparison 4: Intralesional betamethasone versus saline (long-term), Outcome 2: Discontinuation from treatment

Study or Subgroup	Betamethasone Events	Total	Saline Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Cipollone 1998	0	15	0	15	Not estimable	



Analysis 4.3. Comparison 4: Intralesional betamethasone versus saline (long-term), Outcome 3: Subjective patient-reported change in penile curvature

Study or Subgroup	Betamethasone Events	Betamethasone Total	Saline Events	Saline Total	Risk Ratio M-H, Random, 95% CI
Cipollone 1998	3	15	4	15	0.75 [0.20 , 2.79]

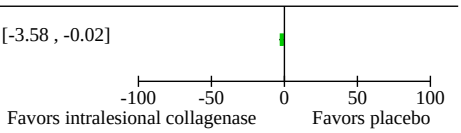


Comparison 5. Intralesional collagenase versus placebo (short-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.2 Degree of penile curvature	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

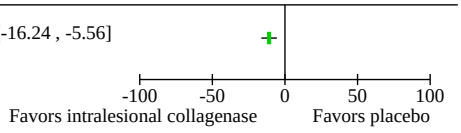
Analysis 5.1. Comparison 5: Intralesional collagenase versus placebo (short-term), Outcome 1: Quality of life

Study or Subgroup	Intralesional collagenase Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
Gelbard 2012	-2.55	4.58	100	-0.75	4.58	34	-1.80 [-3.58 , -0.02]



Analysis 5.2. Comparison 5: Intralesional collagenase versus placebo (short-term), Outcome 2: Degree of penile curvature

Study or Subgroup	Intralesional collagenase Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
Gelbard 2012	-16.3	14.6	100	-5.4	13.8	36	-10.90 [-16.24 , -5.56]



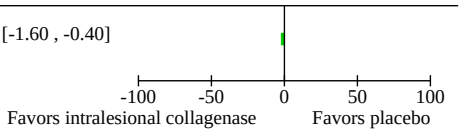
Comparison 6. Intralesional collagenase versus placebo (long term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Treatment-related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.3 Degree of penile curvature	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.4 Discontinuation from treatment	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.5 Subjective patient-reported change in penile curvature	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.6 Improvement in penile pain	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

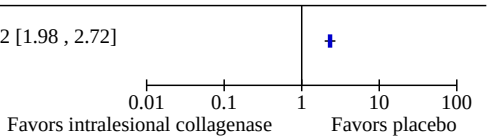
Analysis 6.1. Comparison 6: Intralesional collagenase versus placebo (long term), Outcome 1: Quality of life

	Intralesional collagenase			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Gelbard 2013	-2.8	3.8	401	-1.8	3.5	211	-1.00 [-1.60 , -0.40]	



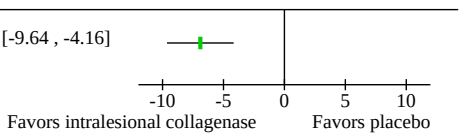
Analysis 6.2. Comparison 6: Intralesional collagenase versus placebo (long term), Outcome 2: Treatment-related adverse effects

	Intralesional collagenase		Placebo		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	M-H, Random, 95% CI	M-H, Random, 95% CI
Gelbard 2013	464	551	102	281	2.32 [1.98 , 2.72]	



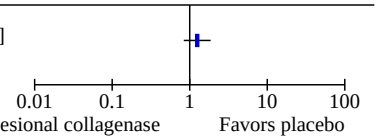
Analysis 6.3. Comparison 6: Intralesional collagenase versus placebo (long term), Outcome 3: Degree of penile curvature

	Intralesional collagenase			Placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Gelbard 2013	33.1	16.8	401	40	16.2	211	-6.90 [-9.64 , -4.16]	



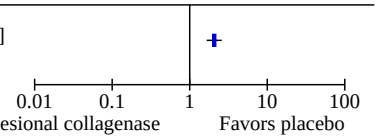
Analysis 6.4. Comparison 6: Intralesional collagenase versus placebo (long term), Outcome 4: Discontinuation from treatment

Study or Subgroup	Intralesional collagenase Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Gelbard 2013	74	555	30	281	1.25 [0.84 , 1.86]



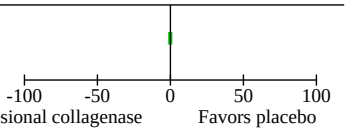
Analysis 6.5. Comparison 6: Intralesional collagenase versus placebo (long term), Outcome 5: Subjective patient-reported change in penile curvature

Study or Subgroup	Intralesional collagenase Events	Total	Placebo Events	Total	Risk Ratio M-H, Random, 95% CI
Gelbard 2013	244	401	62	211	2.07 [1.66 , 2.59]



Analysis 6.6. Comparison 6: Intralesional collagenase versus placebo (long term), Outcome 6: Improvement in penile pain

Study or Subgroup	Intralesional collagenase Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Random, 95% CI
Gelbard 2013	-4.4	5.6	401	-4.3	4.8	211	-0.10 [-0.95 , 0.75]

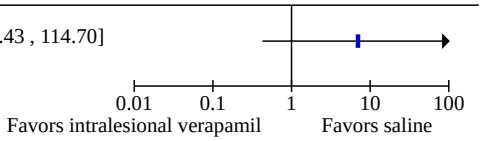


Comparison 7. Intralesional verapamil versus saline (long-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Patient-reported ability to have intercourse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.2 Treatment-related adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.3 Degree of penile curvature	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.4 Subjective patient-reported change in penile curvature	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

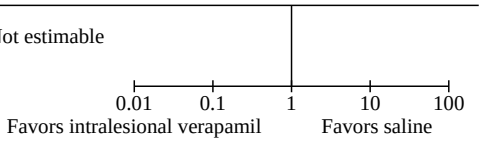
Analysis 7.1. Comparison 7: Intralesional verapamil versus saline (long-term), Outcome 1: Patient-reported ability to have intercourse

Study or Subgroup	Intralesional verapamil Events	Total	Saline Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rehman 1998	3	7	0	7	7.00 [0.43 , 114.70]	



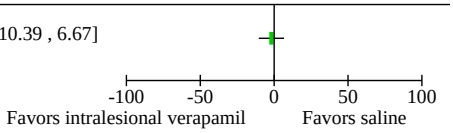
Analysis 7.2. Comparison 7: Intralesional verapamil versus saline (long-term), Outcome 2: Treatment-related adverse effects

Study or Subgroup	Intralesional verapamil Events	Total	Saline Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rehman 1998	0	7	0	7	Not estimable	



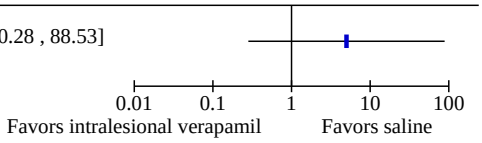
Analysis 7.3. Comparison 7: Intralesional verapamil versus saline (long-term), Outcome 3: Degree of penile curvature

Study or Subgroup	Intralesional verapamil Mean	SD	Total	Saline Mean	SD	Total	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Rehman 1998	29.57	7.3	7	31.43	8.9	7	-1.86 [-10.39 , 6.67]	



Analysis 7.4. Comparison 7: Intralesional verapamil versus saline (long-term), Outcome 4: Subjective patient-reported change in penile curvature

Study or Subgroup	Intralesional verapamil Events	Total	Saline Events	Total	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rehman 1998	2	7	0	7	5.00 [0.28 , 88.53]	

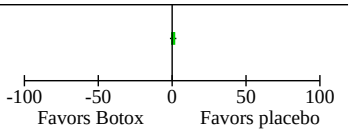


Comparison 8. Intralesional Botox versus placebo (short-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8: Intralesional Botox versus placebo (short-term), Outcome 1: Quality of life

Study or Subgroup	Botox Mean	Botox SD	Botox Total	Control Mean	Control SD	Control Total	Mean Difference IV, Random, 95% CI
Antar 2019	0	1.78	6	-0.67	2.048	6	0.67 [-1.50 , 2.84]

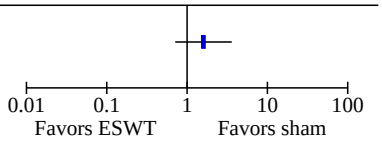


Comparison 9. ESWT versus sham (short-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Patient-reported ability to have intercourse	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.2 Quality of life	2	130	Mean Difference (IV, Random, 95% CI)	3.10 [1.57, 4.64]
9.3 Treatment-related adverse effects	3	166	Risk Ratio (M-H, Random, 95% CI)	2.73 [0.74, 10.14]
9.4 Degree of penile curvature	3	166	Mean Difference (IV, Random, 95% CI)	-2.84 [-7.35, 1.67]
9.5 Discontinuation from treatment	4	268	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.06, 5.65]
9.6 Subjective patient-reported change in penile curvature	2	129	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.72, 1.87]
9.7 Improvement in penile pain	3	151	Mean Difference (IV, Random, 95% CI)	-1.09 [-2.22, 0.04]

Analysis 9.1. Comparison 9: ESWT versus sham (short-term), Outcome 1: Patient-reported ability to have intercourse

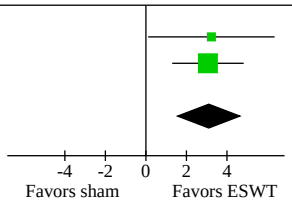
Study or Subgroup	ESWT Events	ESWT Total	Sham Events	Sham Total	Risk Ratio M-H, Random, 95% CI
Hatzichristodoulou 2013	8	13	5	13	1.60 [0.71 , 3.60]



Analysis 9.2. Comparison 9: ESWT versus sham (short-term), Outcome 2: Quality of life

Study or Subgroup	ESWT Mean	ESWT SD	ESWT Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Random, 95% CI
Mortensen 2021	0.17	3	14	-3.06	5.5	16	24.2%	3.23 [0.11 , 6.35]
Palmieri 2009	22.68	4.5	50	19.62	4.5	50	75.8%	3.06 [1.30 , 4.82]
Total (95% CI)			**64**			**66**	**100.0%**	**3.10 [1.57 , 4.64]**

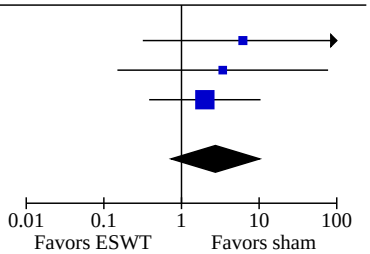
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 3.96 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 9.3. Comparison 9: ESWT versus sham (short-term), Outcome 3: Treatment-related adverse effects

Study or Subgroup	ESWT Events	ESWT Total	Sham Events	Sham Total	Weight	Risk Ratio M-H, Random, 95% CI
Chitale 2010	2	16	0	20	19.5%	6.18 [0.32 , 120.18]
Mortensen 2021	1	14	0	16	17.6%	3.40 [0.15 , 77.34]
Palmieri 2009	4	50	2	50	62.9%	2.00 [0.38 , 10.43]
Total (95% CI)		**80**		**86**	**100.0%**	**2.73 [0.74 , 10.14]**
Total events:	7		2			

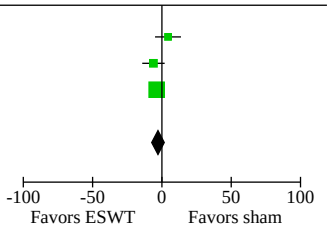
Heterogeneity: Tau² = 0.00; Chi² = 0.45, df = 2 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 9.4. Comparison 9: ESWT versus sham (short-term), Outcome 4: Degree of penile curvature

Study or Subgroup	ESWT Mean	ESWT SD	ESWT Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Random, 95% CI
Chitale 2010	-0.9	16	16	-5.3	11.6	20	18.0%	4.40 [-4.94 , 13.74]
Mortensen 2021	-12.7	13	14	-6.6	8.9	16	22.4%	-6.10 [-14.19 , 1.99]
Palmieri 2009	27.45	8.11	50	31.25	6.74	50	59.6%	-3.80 [-6.72 , -0.88]
Total (95% CI)			**80**			**86**	**100.0%**	**-2.84 [-7.35 , 1.67]**

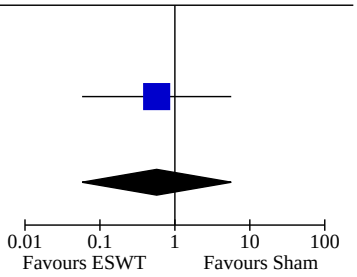
Heterogeneity: Tau² = 6.66; Chi² = 3.18, df = 2 (P = 0.20); I² = 37%
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 9.5. Comparison 9: ESWT versus sham (short-term), Outcome 5: Discontinuation from treatment

Study or Subgroup	ESWT Events	ESWT Total	Sham Events	Sham Total	Weight	Risk Ratio M-H, Random, 95% CI
Chitale 2010	0	16	0	20		Not estimable
Hatzichristodoulou 2013	0	51	0	51		Not estimable
Mortensen 2021	1	14	2	16	100.0%	0.57 [0.06 , 5.65]
Palmieri 2009	0	50	0	50		Not estimable
Total (95% CI)		**131**		**137**	**100.0%**	**0.57 [0.06 , 5.65]**
Total events:	1		2			

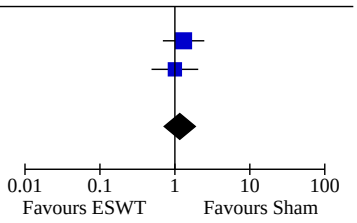
Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Analysis 9.6. Comparison 9: ESWT versus sham (short-term), Outcome 6: Subjective patient-reported change in penile curvature

Study or Subgroup	ESWT Events	ESWT Total	Sham Events	Sham Total	Weight	Risk Ratio M-H, Random, 95% CI
Hatzichristodoulou 2013	16	50	12	49	56.0%	1.31 [0.69 , 2.47]
Mortensen 2021	7	14	8	16	44.0%	1.00 [0.49 , 2.05]
Total (95% CI)		**64**		**65**	**100.0%**	**1.16 [0.72 , 1.87]**
Total events:	23		20			

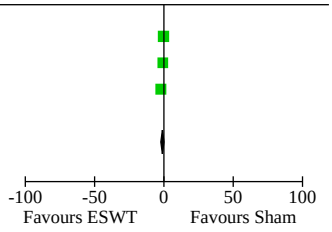
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable



Analysis 9.7. Comparison 9: ESWT versus sham (short-term), Outcome 7: Improvement in penile pain

Study or Subgroup	ESWT Mean	ESWT SD	ESWT Total	Sham Mean	Sham SD	Sham Total	Weight	Mean Difference IV, Random, 95% CI
Chitale 2010	-1.1	1.8	16	-0.8	1.8	20	34.9%	-0.30 [-1.48 , 0.88]
Mortensen 2021	-0.9	2.1	14	-0.1	1.5	16	31.9%	-0.80 [-2.12 , 0.52]
Palmieri 2009	0.46	2.97	42	2.66	2.97	43	33.2%	-2.20 [-3.46 , -0.94]
Total (95% CI)			**72**			**79**	**100.0%**	**-1.09 [-2.22 , 0.04]**

Heterogeneity: Tau² = 0.59; Chi² = 4.86, df = 2 (P = 0.09); I² = 59%
Test for overall effect: Z = 1.89 (P = 0.06)
Test for subgroup differences: Not applicable



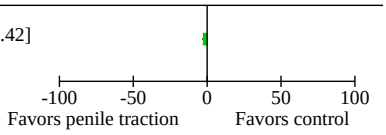
Comparison 10. Penile traction therapy versus no treatment (short-term)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.2 Treatment-related adverse events	1	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Degree of penile curvature	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.4 Discontinuation from treatment	2	182	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.31, 2.36]
10.5 Improvement in penile pain	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10: Penile traction therapy versus no treatment (short-term), Outcome 1: Quality of life

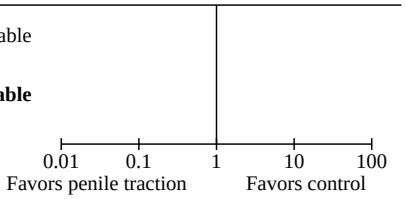
	Penile traction			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Ziegelmann 2019	-2.4	3.4	59	-0.9	4.2	23	-1.50 [-3.42 , 0.42]	



Analysis 10.2. Comparison 10: Penile traction therapy versus no treatment (short-term), Outcome 2: Treatment-related adverse events

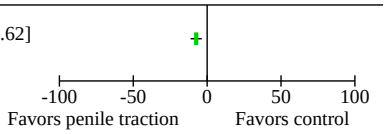
	Penile traction		Control			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Ziegelmann 2019	0	63	0	27		Not estimable	
Total (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 10.3. Comparison 10: Penile traction therapy versus no treatment (short-term), Outcome 3: Degree of penile curvature

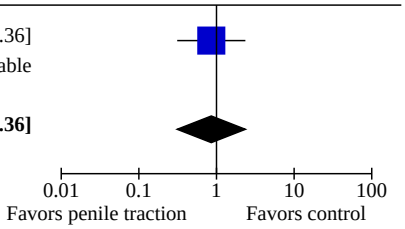
	Penile traction			Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Ziegelmann 2019	-8.5	10.1	62	-1.1	7.5	27	-7.40 [-11.18 , -3.62]	



Analysis 10.4. Comparison 10: Penile traction therapy versus no treatment (short-term), Outcome 4: Discontinuation from treatment

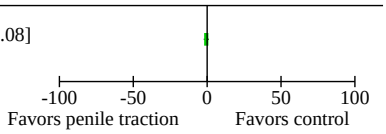
Study or Subgroup	Penile traction Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Moncada 2019	6	46	7	46	100.0%	0.86 [0.31 , 2.36]
Ziegelmann 2019	0	63	0	27		Not estimable
Total (95% CI)		**109**		**73**	**100.0%**	**0.86 [0.31 , 2.36]**
Total events:	6		7			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.30 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 10.5. Comparison 10: Penile traction therapy versus no treatment (short-term), Outcome 5: Improvement in penile pain

Study or Subgroup	Penile traction Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Random, 95% CI
Ziegelmann 2019	-1.4	3.2	59	-0.8	3.6	23	-0.60 [-2.28 , 1.08]



ADDITIONAL TABLES

Table 1. Inclusion and exclusion criteria

Study	Intervention	Inclusion criteria	Exclusion criteria
Antar 2019	Botox	• Stable phase PD	• Active phase PD, multiple plaques, calcified plaques
Chitale 2010	Shock wave lithotripsy	• Stable penile deformity secondary to PD affecting their ability to perform sexual intercourse and/or quality of life due to penile angulation • Recent onset of painless deformity of the penis on erection, and stable for > 6 months • Pain and/or angulation of the penis on erection • Difficult intercourse due to penile curvature, and partner dissatisfaction • A degree of erectile dysfunction (partial) associated with penile deformity • Palpable plaque along the penis with penile deformity • Aged > 18 years	• Congenital curvature of the penis • Previous treatment for PD (surgical/medical) • Patient on warfarin • Patient with total erectile dysfunction in need of therapy for erectile dysfunction
Cipollone 1998	Betamethasone	Not reported	• Presence of medical disease such as: peptic ulcer, acute gastritis or esophagitis, diabetes mellitus, osteo-

Table 1. Inclusion and exclusion criteria *(Continued)*

			porosis, glaucoma, cataract, severe arterial hypertension, and cardiovascular insufficiency
Gelbard 2012	Collagenase	• Healthy, heterosexual men over age 18 in a stable relationship with a partner/spouse (for at least 3 months) • Diagnosis of PD for at least 6 months • Penile curvature of at least 30 degrees in the dorsal, lateral, or dorsal/lateral plane (must have been possible to delineate the single plane of maximal curvature for evaluation) • Functional difficulty related to PD (e.g. erectile dysfunction or difficulty with intromission)	• Men with penile curvature of less than 30 or greater than 90 degrees • Calcified plaque • Severe pain during penile palpation (as determined by the investigator), • Allergy to collagenase or other medication required by the protocol, • Hypertension • Other penile abnormalities such as chordee or hypospadias • Erectile dysfunction unresponsive to phosphodiesterase type 5 inhibitors • Previous PD treatment (surgery or oral agents within 4 weeks; injectional medical therapies within 3 months; mechanical devices within 2 weeks) • Failure to respond with full erection to prostaglandin E1 during malformation measurement
Gelbard 2013	Collagenase	• Healthy, heterosexual men over age 18 in a stable relationship with a partner/spouse (for at least 3 months) • Diagnosis of PD for at least 6 months • Penile curvature of at least 30 degrees in the dorsal, lateral, or dorsal/lateral plane (must have been possible to delineate the single plane of maximal curvature for evaluation) • Functional difficulty related to PD (e.g. erectile dysfunction or difficulty with intromission)	• Men with penile curvature of less than 30 or greater than 90 degrees • Calcified plaque • Severe pain during penile palpation (as determined by the investigator) • Allergy to collagenase or other medication required by the protocol • Hypertension • Other penile abnormalities such as chordee or hypospadias • Erectile dysfunction unresponsive to phosphodiesterase type 5 inhibitors • Previous PD treatment (surgery or oral agents within 4 weeks; injectional medical therapies within 3 months; mechanical devices within 2 weeks) • Investigational drug or treatment (including collagenase *Clostridium histolyticum*) within 30 days before start of the study • Anticoagulant medication (except for ≤ 165 mg aspirin daily or ≤ 800 mg of over-the-counter NSAIDs daily) during the 7 days before each dose of study drug, at any time • Failure to respond with full erection to prostaglandin E1 during malformation measurement
Hatzichristodoulou 2013	Shock wave lithotripsy	• Men with previous unsuccessful oral medical therapy • Age ≥ 18 years, and plaques and/or pain at erection and/or deviation	• Men with prior penile surgery and erectile dysfunction not responding to phosphodiesterase-type-5 inhibitors or intracavernous injections

Table 1. Inclusion and exclusion criteria *(Continued)*

		• Disease duration ≥ 12 months • Unchanged symptoms (deviation, pain, and plaques) for ≥ 3 months	
Hellstrom 2006	Interferon alpha-2B	• Men age 18 years or older with a history of PD of 12 months or more • Single plaque • At least 30 degree penile curvature on erection	• Calcified plaque
Moncada 2019	Penile traction	• Patients diagnosed with PD for at least 1 year • Without ED • No significant pain • Unidirectional curvature of at least 45° • Stable for at least 3 months prior to inclusion into the study	• Hourglass deformity • Complex curvatures or areas of tunical indentation • Patients submitted to previous collagenase or any other injectional treatments
Mortensen 2021	Shock wave lithotripsy	• Patients diagnosed with PD for at least 6 months • Stable disease phase defined as no curvature change within last 3 months • Men aged 18 to 80 years • Penile curvature between 20 and 90 degrees	• Previous penile surgery • Previous ESWT treatment history
Palmieri 2009	Shock wave lithotripsy	• Men aged between 18 and 75 years with PD not > 12 months • Only one plaque demonstrated by basal and dynamic sonography and by palpation with a maximum size of 3.75 cm^2 • No previous medical or surgical therapies for PD • Stable sexual relationship • Presence of painful erections (score ≥ 5 on a VAS with a score ranging from 0 to 10) • Erectile dysfunction, and penis recurvatum	• Men with medical issues such as: blood coagulation disorders, cardiac pacemaker, lower urinary tract infections, and vascular disorders in the path of the shock waves
Rehman 1998	Verapamil	• Age range 35 to 70 years with clinical evidence of PD, that is, pain and plaque along with deformity of the penis of at least 1-year duration • Discontinuation of any previous oral or other medication for PD for at least 3 months	• History of calcium channel blocker therapy or therapy interfering with calcium channel blockers
Soh 2010	Nicardipine	• Men with PD with erectile dysfunction	Not reported
Weidner 2005	POTABA	• Men with a history of a maximum of 12 months • No prior treatment • No evidence of calcified plaques	• Men with a history of prior treatment • Symptoms of more than 12 months duration • Sonographic evidence of calcification

Table 1. Inclusion and exclusion criteria *(Continued)*

			• No response to the intracavernous injection test • Diseases such as: diabetes mellitus, compensated nephropathy, and chronic gastric and bowel diseases.
Ziegelmann 2019	Penile traction	• PD • Age greater than 18 years • More than 30 degrees of curvature	• Stretched penile length less than 7 cm • Severe diabetes (end organ failure)

ED: erectile dysfunction; ESWT: extracorporeal shock wave treatment; NSAIDs: non-steroidal anti-inflammatory drugs; PD: Peyronie's disease; POTABA: potassium paraaminobenzoate; VAS: visual analog scale

Table 2. Study characteristics

Study	Country	No.	Route	Intervention	Comparison	Baseline curvature	Treatment duration
Antar 2019	USA	12	Injectional	Botox	Placebo	Not reported	16 weeks
Chitale 2010	UK	36	Shock wave	Shock wave lithotripsy	Sham	24.9 to 33.3 degrees	6 weeks
Cipollone 1998	Italy	30	Injectional	Betamethasone	Saline	Not reported	12 months
Gelbard 2012	USA	147	Injectional	Collagenase	Placebo	At least 30 degrees	18 weeks
Gelbard 2013	USA/Australia	836	Injectional	Collagenase	Placebo	At least 30 degrees	24 weeks
Hatzichristodoulou 2013	Germany	102	Shock wave	Shock wave lithotripsy	Placebo	43 to 44 degrees	6 weeks
Hellstrom 2006	USA	117	Injectional	Interferon alpha-2B	Placebo	49.9 to 50.9 degrees	12 weeks
Moncada 2019	Spain/India/Germany/USA	93	Traction	Penile traction	Sham	At least 45 degrees	12 weeks
Mortensen 2021	Denmark	32	Shock wave	Shock wave lithotripsy	Sham	45 to 47.6 degrees	5 weeks
Palmieri 2009	Italy	100	Shock wave	Shock wave lithotripsy	Placebo	28.9 to 29.5	4 weeks
Rehman 1998	USA	14	Injectional	Verapamil	Saline	33.6 to 37.7	6 months
Soh 2010	Japan	74	Injectional	Nicardipine	Placebo	30.9 to 32.1 degrees	10 weeks
Weidner 2005	Germany	103	Oral	POTABA	Placebo	Not reported	12 months
Ziegelmann 2019	USA	110	Traction	Penile traction	Control	At least 30 degrees	3 months

POTABA: potassium paraaminobenzoate; UK: United Kingdom; USA: United States of America

Table 3. Overview of outcomes

	Patient-reported ability to have intercourse	Quality of life	Treatment-related adverse effects	Degree of penile curvature	Discontinuation from treatment
Oral agents[1]					
Potassium para-aminobenzoate (short-term)	May result in little to no change	No evidence	Very uncertain	No evidence	Very uncertain
Injectional agents[1]					
Injectional interferon alpha-2B (short-term)	No evidence	No evidence	No evidence	Very uncertain	Very uncertain
Injectional nicardipine (long-term)	No evidence	No evidence	Very uncertain	Very uncertain	Very uncertain
Injectional betamethasone (long-term)	No evidence	No evidence	Very uncertain	No evidence	Very uncertain
Injectional collagenase (short-term)	No evidence	May result in little to no change	No evidence	May result in little to no change	No evidence
Injectional collagenase (long-term)	No evidence	Likely results in little to no change	Probably increased	Likely results in little to no change	May increase
Injectional verapamil (short-term)	Very uncertain	No evidence	Very uncertain	Very uncertain	No evidence
Injectional Botox (short-term)	No evidence	Very uncertain	No evidence	No evidence	No evidence
Device-based application[1]					
ESWT (short-term)	Very uncertain	May result in little to no change	Very uncertain	May result in little to no change	Very uncertain
Penile traction (short-term)	No evidence	Very uncertain	Very uncertain	Very uncertain	Very uncertain

[1]Comparator was placebo unless otherwise indicated.
ESWT: extracorporeal shock wave therapy

APPENDICES

Appendix 1. Search strategies

	Search strategy for MEDLINE (PubMed)
#1	"Penile Induration/therapy"[Mesh]

(Continued)

#2	"Penile Fibromatosis"
#3	"Peyronie's Disease"
#4	"Peyronies Disease"
#5	"Plastic Induration of the Penis"
#6	"Fibrous Cavernitides"
#7	"Fibrous Cavernitis"
#8	"Peyronie Disease"
#9	Therapy
#10	Intervention
#11	Treatment
#12	"Randomized Controlled Trial" [Publication Type]
#13	“randomized control trial”
#14	"Controlled Clinical Trial" [Publication Type]
#15	“controlled clinical trial”
#16	“clinical trial”
#17	"Pragmatic Clinical Trial" [Publication Type]
#18	“pragmatic clinical trial”
#19	“clinical trial” [publication type]
#20	“clinical trial”
#21	"Observational Study" [Publication Type]
#22	“observational study”
#23	"Cohort Studies"[Mesh]
#24	“cohort studies”
#25	randomized[tiab]
#26	randomly[tiab]
#27	trial[tiab]
#28	groups[tiab]
#29	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8

(Continued)

#30	#9 or #10 #11
#31	#12 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28
#32	#29 AND #30
#33	#32 OR #1
#34	#33 AND #31

	Search strategy for Cochrane Library (Wiley) (CENTRAL, DARE, CCR, Cochrane Database of Systematic Reviews)
#1	MeSH descriptor: [Penile Induration] explode all trees and with qualifier(s): [Therapy - TH]
#2	"Penile Fibromatosis"
#3	"Peyronie's Disease"
#4	"Peyronies Disease"
#5	"Plastic Induration of the Penis"
#6	"Fibrous Cavernitides"
#7	"Fibrous Cavernitis"
#8	"Peyronie Disease"
#9	"Penile Fibromatosis"
#10	Treatment
#11	Intervention
#12	Therapy
#13	“randomized control trial”
#14	“controlled clinical trial”
#15	“clinical trial”
#16	“pragmatic clinical trial”
#17	“observational study”
#18	“cohort studies”
#19	randomized

(Continued)

#20	randomly
#21	trials
#22	groups
#23	#2 OR #3 OR #$ OR #5 OR #6 OR #7 OR #8 OR #9
#24	#10 OR #11 OR #12
#25	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#26	#23 AND #24
#27	#26 AND #25

	Search strategy for MEDLINE (PubMed)
#1	Peyronie disease/de
#2	"Penile Fibromatosis"
#3	"Peyronie's Disease"
#4	"Peyronies Disease"
#5	"Plastic Induration of the Penis"
#6	"Fibrous Cavernitides"
#7	"Fibrous Cavernitis"
#8	"Peyronie Disease"
#9	“Penile induration”
#10	“penis induration plastica”
#11	“penis plasticus”
#12	“penile fibromatosis”
#13	“penis strabismus”
#14	Therapy/de
#15	Intervention
#16	Treatment
#17	Randomized Controlled Trial/de

(Continued)

#18	“randomized control trial”
#19	Controlled Clinical Trial/de
#20	“controlled clinical trial”
#21	“clinical trial”
#22	Pragmatic Trial/de
#23	“pragmatic clinical trial”
#24	clinical trial/de
#25	“clinical trial”
#26	Observational Study/de
#27	“observational study”
#28	Cohort Studies/de
#29	“cohort studies”
#30	randomized
#31	randomly
#32	trial
#33	groups
#34	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#35	#14 OR #15 OR #16
#36	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
#37	#34 AND #35
#38	#37 AND #36

	Search strategy for Web of Science Search (Thompson Reuters)
#1	TS=”peyronie’s disease”
#2	TS = “peyronies disease”
#3	TS="Plastic Induration of the Penis"
#4	TS=”penile induration”

(Continued)

#5	TS=”penile fibromatosis”
#6	TS="Fibrous Cavernitides"
#7	TS="Fibrous Cavernitis"
#8	TS=”Peyronie Disease”
#9	TS=Therapy
#10	TS=Intervention
#11	TS=Treatment
#12	TS=“randomized control trial”
#13	TS=“controlled clinical trial”
#14	TS=“clinical trial”
#15	TS=“pragmatic clinical trial”
#16	TS=“observational study”
#17	TS=“cohort studies”
#18	TS=randomized
#19	TS=randomly
#20	TS=trial
#21	TS=groups
#22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#23	#9 OR #10 OR #11
#24	#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#25	#22 AND #23
#26	#25 AND #24

HISTORY

Protocol first published: Issue 5, 2016

CONTRIBUTIONS OF AUTHORS

Joel Rosenberg (JR): trial selection, data analysis, data interpretation, and review drafting and update.

Eu Chang Hwang (ECH): protocol drafting, search strategy development, trial selection, data extraction, data analysis, data interpretation, review drafting, and review update.

Michael C Risk (MCR): data interpretation and provision of critical content expertise that informed the review.

Jae Hung Jung (JHJ): protocol drafting, search strategy development, acquiring trial reports, trial selection, data extraction, data analysis, data interpretation, review drafting, and review update.

Onuralp Ergun (OE): trial selection, data extraction, data analysis, data interpretation, review drafting, and review update.

Yooni Blair (YB): data interpretation and provision of critical content expertise that informed the review.

Mary E Edwards (MEE): search strategy development and execution; study deduplication and periodic updates.

Philipp Dahm (PD): protocol drafting, search strategy review/oversight, trial selection, data interpretation, certainty of evidence ratings, and general oversight.

DECLARATIONS OF INTEREST

JR: none known.

ECH is a Contact Editor for Cochrane Urology, however he was not involved in the editorial process of this review.

MCR is a Contact Editor for Cochrane Urology, however he was not involved in the editorial process of this review.

JHJ is a Contact Editor for Cochrane Urology, however he was not involved in the editorial process of this review.

OE is a Fellow for Cochrane Urology, however he was not involved in the editorial process of this review.

YB: none known.

MEE: none known.

PD is the Co-ordinating Editor of Cochrane Urology, however he was not involved in the editorial process of this review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol with differences as described here.

- We found eligible studies on colchicine, vitamin E and propionyl-L-carnitine (separately or in combination), omega-3 coenzyme Q10, pentoxifylline, and injectional verapamil. All were small and published by the same (single) author who has had to withdraw multiple publications over concerns about data falsification. After consultation with the Cochrane Urology Editorial Group and the Cochrane Cancer Network, we decided to exclude these studies.
- Based on feedback from clinical peer reviewers, we removed a number of interventions as not clinically relevant to today's practice. The selection of now included comparisons is based on a survey of content experts.
- Based on content expert feedback, we decided to remove the two last (of seven) outcomes listed in the protocol (Pagliara 2016), according to priority, from the summary of findings tables. Discontinuation from treatment was not felt to be that important in this setting and penile pain is an outcome most relevant to the acute phase of the disease, in which these treatments are typically not indicated. The results for these outcomes are, however, fully reported in the text.
- We revised the objectives to account for the fact that we investigated a broad set of outcomes.
- We have since specified in the methods how outcomes were assessed.

NOTES

Parts of the Methods section and Appendix 1 of this protocol are based on a standard template developed by Cochrane Metabolic and Endocrine Disorders that has been modified and adapted for use by Cochrane Urology.

INDEX TERMS

Medical Subject Headings (MeSH)

*Erectile Dysfunction; Pain; *Penile Induration [therapy]; Quality of Life; Randomized Controlled Trials as Topic; Verapamil

MeSH check words

Humans; Male