



Mens Health
**INTERNATIONAL
SURGICAL CENTER**
SWITZERLAND

5th Emirates International

UROLOGICAL
Conference

Medical and Non-Surgical Treatment of Peyronie's Disease

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www.mhisc.ch

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Natural History

		Gelbard 1990	Mulhall 2006	Mulhall 2014
	n	97	246	176
Follow up		9 yrs	>18mths	>12mths
Pain resolution		100%	89%	-
Deformity	Worse %	42	48	21
	Stable %	45	40	67
	Better %	13	12	12
				Duration<6/12 Increasing Age

Gelbard JUrol 1992
 Mulhall JUrol 2006
 Mulhall BJUI 2014

The non-surgical treatment of Peyronie's Disease

Therapy	Author	Date
Mercury + Mineral water	de la Peyronie	1743*
Potassium iodide	Ricord	1844*
Electricity	Van Buren	1864*
Bromides + Hyperthermia	Hodgen	1876*
Sulphur	Dubuc	1890*
Copper sulphate	O'Zoux	1896*
Salicylates + Thiosinamin	Sachs	1901*
Arsenic	Passover	1902*
Fibrolysin	Mendel	1907*
Ionization	Lavenant	1910*
Milk	Van der Pool	1911*
X-radiation	Lavenant	1911*
Ultraviolet light	LeFur	1912*
Trypsin injection	Sonntag	1922*
Radium	Kumer	1922*
Diathermy	Wesson	1943
Vitamin E	Scardino and Scott	1949
Cortisone injection	Teasley	1954
Hyaluronidase + Steroid injection	Bodner et al	1954
Potassium para-aminobenzoate	Zarafonetis and Horrax	1959
Histamine iontophoresis	Whalen	1960

* = Polkey, 1928

The non-surgical treatment of Peyronie's Disease

Therapy	Author	Date
Prednisolone	Chesney	1963
Ultrasound	Heslop et al.	1967
Dimethyl sulphoxide	Persky and Stewart	1967
Steroid iontophoresis	Rothfield and Murray	1967
Procarbazine	Aboulter & Benassayag	1970
Parathormone injection	Morales and Bruce	1975
Orgotein	Bartsch et al.	1981
b-Aminopropionitile	Gelbard et al.	1983
Collagenase injection	Gelbard et al.	1985
Laser ablation	Puente de la Vega	1985
Prostacyclin	Strachan and Pryor	1988
Lithotripsy	Bellorofonte et al.	1989
Interferon a2b	Benson et al	1991
Tamoxifen	Ralph et al	1992
Verapamil	Levine et al.	1994
Colchicine	Akkus et al.	1994
Propoleum	Lemourt	1998
Acetyl L Carnitnine	Biagotti	2001
Pentoxifylline	Brant	2006
Tadalafil	Porst	2009
Coenzyme Q	Safrinajad	2010
EMU /nicardipine/ SOD	Levine	2015

Oral Agents (I)

Drug	MOA	RCTs	Conclusions	AUA 2015 Guidelines
NSAIDS	Anti-inflammatory	None		Recommended for pain management Expert Opinion
Vitamin E [1,2]	Antioxidant effect scavenges free radicals like reactive oxygen species); DNA repair; immune modulation	1 (n=23)	Inexpensive; Possibly effective; Reasonable Rx awaiting disease stabilization; Few AEs	Not recommended Evidence B
Carnitines¹	Acetyl - l carnitine and propionyl-l carnitine; inhibits acetyl CoA; prevents cutaneous inflammation (in animals); protects small arteries from chemical vasculitis	2	RCTs suggest efficacy	Not recommended Evidence B
Vitamin E + propionyl-l-Carnitine [3]	Combined MOAs of Vitamin E and propionyl-l-carnitine; Vit E alone, PLC alone, or Vit E + PLC, vs. placebo	1 (n=236)	No significant improvement in pain, curvature or plaque size vs PBO	Not recommended Evidence B

1. Trost LW, et al. Drugs. 2007;67(4):527-545.
2. Paulis G et al. Andrology 2013;1(1): 120-8
3. Safarinejad MR, et al. J Urol. 2007;178(4 Pt 1):1398-1403.
4. Nehra A. et al. J Urol. 2015 Sep;194(3):745-53

Oral Agents (II)

Drug	MOA	RCT	Conclusions	AUA 2015 Guidelines
POTABA (Para amino benzoate)	Enhancement of oxygen uptake, glucosaminoglycan secretion and monoamine oxidase activity; decreases serotonin activity; decreases fibrosis	1	Expensive; Poorly tolerated; Up to 24 tab QD Effects undetermined; First-line Therapy	Not recommended Evidence B
Colchicine	Antiinflammatory; induces collagenase, binds tubulin, inhibits mobility and adhesion of leukocytes; inhibits mitosis; inhibits collagen synthesis; frequently first- line therapy	None	Inexpensive; Reasonably well- tolerated; Effects undetermined; GI side effects include severe diarrhea	Recommended for pain management Expert Opinion

1. Trost LW et al. Drugs. 2007;67(4):527-545
2. Nehra A. et al. J Urol. 2015 Sep;194(3):745-53

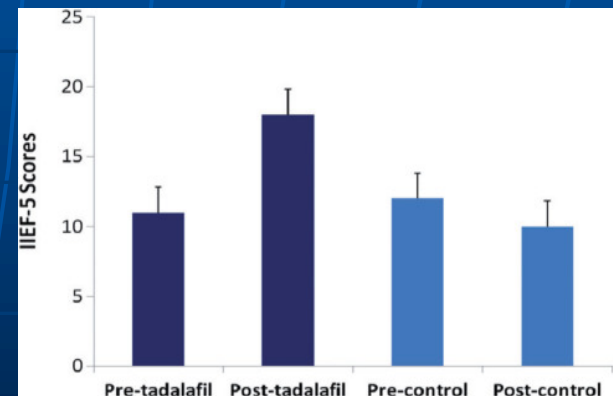
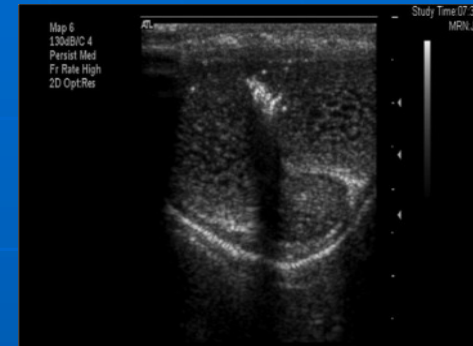
Oral Agents (III)

Drug	MOA	RCTs	Conclusions	AUA 2015 Guidelines
Tamoxifen	Aids release of TGFβ from Fibroblasts w/ blocking of TGFβ receptor sites; down-regulates immune response; decreases fibrinogenesis	1 [1]	Well tolerated; Unlikely to be effective as oral agent	Not recommended Evidence B
Pentoxifylline	Improves capillary blood flow, probably by increasing RBC flexibility; lowers blood viscosity; prevents plaque formation (rat model); cGMP promoter	None		Not recommended Evidence B
PDE-5is	Cyclic GMP acts as an antifibrotic; prolonged use of sildenafil inhibits fibrosis (rat model)	1 [2,3]	Effective treatment for comorbid ED	Not mentioned

1. Trost LW, et al. Drugs. 2007;67(4):527-545
2. Ozturk U et al. Ir J Med Sci 2014; 183(3):449-453
3. Chung E et al. J Sex Med 2011 May;8(5):1472-7
4. Nehra A. et al. J Urol. 2015 Sep;194(3):745-53

PDE5 Inhibitors

- Treatment audit of isolated septal scars at CDU (n=65)
 - 35/65 - tadalafil 2.5mg daily for 6 mo
 - 30/65 - controls
- **Resolution of scar on CDU**
 - **Tadalafil - 24/35 (69%)**
 - **Controls – 10/30 (33%)**
- Improved IIEF 5 with tadalafil
 - 11/25 → 18/25



Pentoxifylline for Peyronie's Disease

- N = 228, 400mg bd 6/12

		Pentox	Placebo	p
	n	101	102	
	Improved	37	9	0.01
Curvature(ICI)	No change	45	71	0.01
	Worse	29	71	
Mean change		23°	-22°	0.003
Pain gone		89%	83%	
Subjective improvement		37%	4.5%	

PD – Injection Therapy

- Steroids
- Verapamil
- Interferon
- Collagenase

Verapamil

- ▶ Calcium channel blocker
- ▶ Decreased collagen production
- ▶ Increased collagenase activity
- ▶ Decreased fibronectin syntheses
- ▶ Decreased fibronectin secretion



Results of Verapamil Treatment

Authors	Patients (n)	Dose (mg)	Duration	Decrease in Curvature (% of pts improved)
Levine, 1994	14	10	Biweekly, 6 Mon	42%
Arena, 1995	39	10	Biweekly, 6 Mon	50% (PD<ly) 10% (PD>ly)
Rehman, 1998	14 (Ver=7; Plc =7)	10	Weekly, 6 Mon	29% Ver. 0% Plc.
Levine, 1997	46	10	Biweekly, 6 Mon	54% ($\mu=27^\circ$)
Levine, 2002	156	10	Biweekly, 6 Mon	60% ($\mu=30^\circ$) 31% stable
Mulhall, 2007	81	10	Biweekly, 3 Mon	22% ($\mu=22^\circ$) 53% stable
Casabe, 2006	33	10	Biweekly, 6 Mon	38% (47% stable) 66% coitus 10% ($u=13.6^\circ$)
Cavallini, 2007	77	10mg/4,10,20 cc	Biweekly, 6 Mon	Best w/20 cc-58% ($u=14^\circ$)
Mulhall 2011	131	10	Bimonthly, 3 mon	26% > 10deg Age >40, curve >30

Results of Intralesional Treatment With IFN- α -2b

Authors	Patients (n)	Dose (Units)	Duration	Decrease in Curvature (% of pts improved)
Wegner, 1995	25	1×10^6	Weekly, 5 Wk	4%
Wegner, 1997	30	3×10^6	Weekly, 3 Wk	3%
Judge, 1997	10	1.5×10^6	3 times/wk, 3wk	60% ($\mu = 20^\circ$)
Ahuja, 1999	21	1×10^6	Biweekly, 6 mon	65%
Astorga, 2000	34	10×10^6	Biweekly, 14 wk	47%
Brake, 2001	23	2×10^6	3 times/wk, 3wk	5%
Dang, 2004 PC	25	2×10^6	Biweekly, 14 wk	67%
Hellstrom, 2006	117 (IFN= 55; Plbo=62)	5×10^6	Biweekly, 14 wk	8.8% Plbo ($\mu = 9^\circ$) 27% IFN ($\mu = 12^\circ$)
Inal, 2006	30	5×10^6	Weekly x 12 ⁺ / ₋ Vit. E vs. Vit. E alone	No objective benefit w/IFN
Hellstrom 2013	127		Biweekly 12 wk	54% (mean 9 °)

XIAFLEX[®]

Collagenase clostridium histolyticum

■ Dosage form

- Sterile lyophilized powder
- Single use vials (0.9 mg)
- Reconstitution in recommended sterile diluent (CaCl₂ and NaCl)



XIAPEX

Current use

- 30°- 90° Dorsal/Lateral curvature
- Non-calcified plaque
- Stable > 1 year

Future use

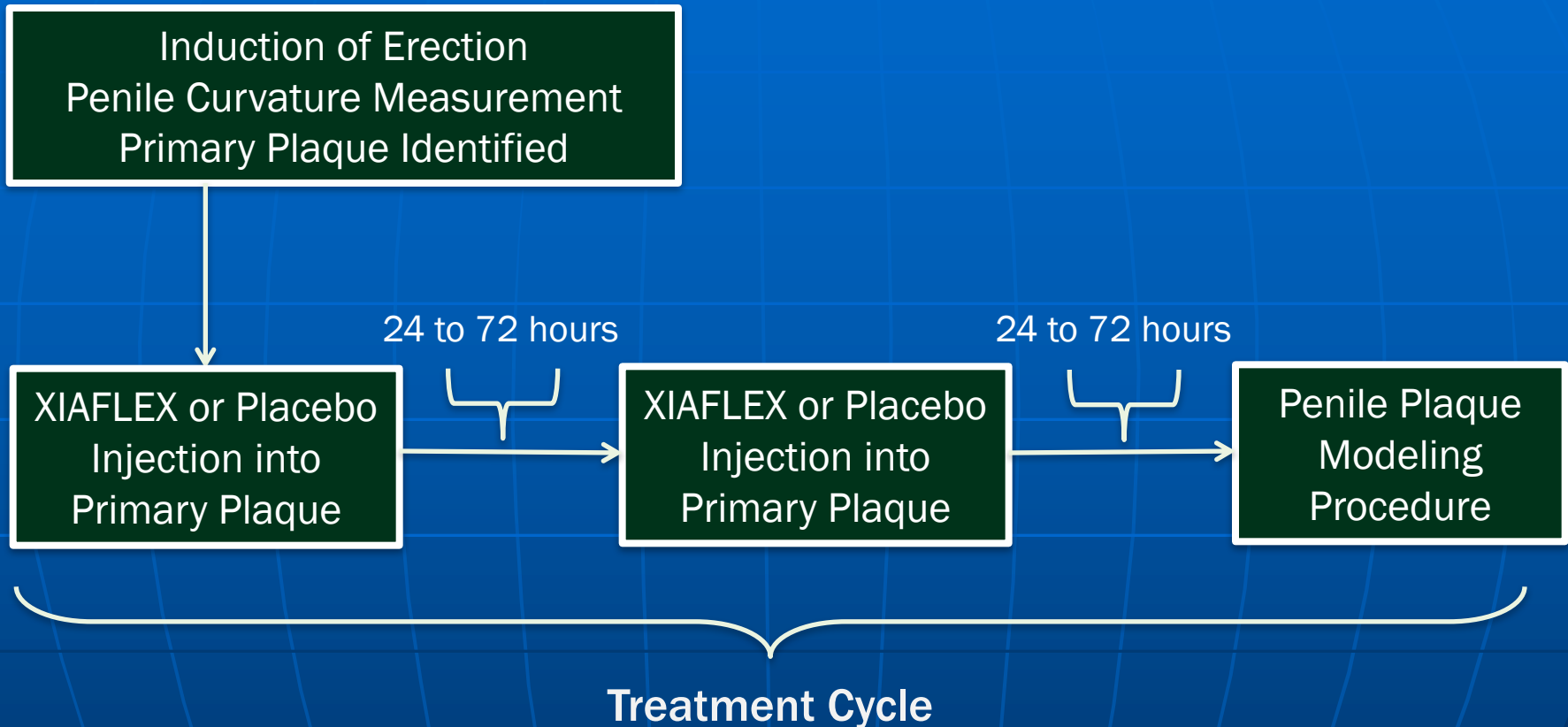
Ventral/septal plaques

Hourglass/indentation

Early disease

Combination with surgery

IMPRESS Treatment Cycles



Subjects may receive up to **four** treatment cycles (up to **8** injections)
Each treatment cycle is separated by 6 weeks

Modelling

- Erect



- Flaccid



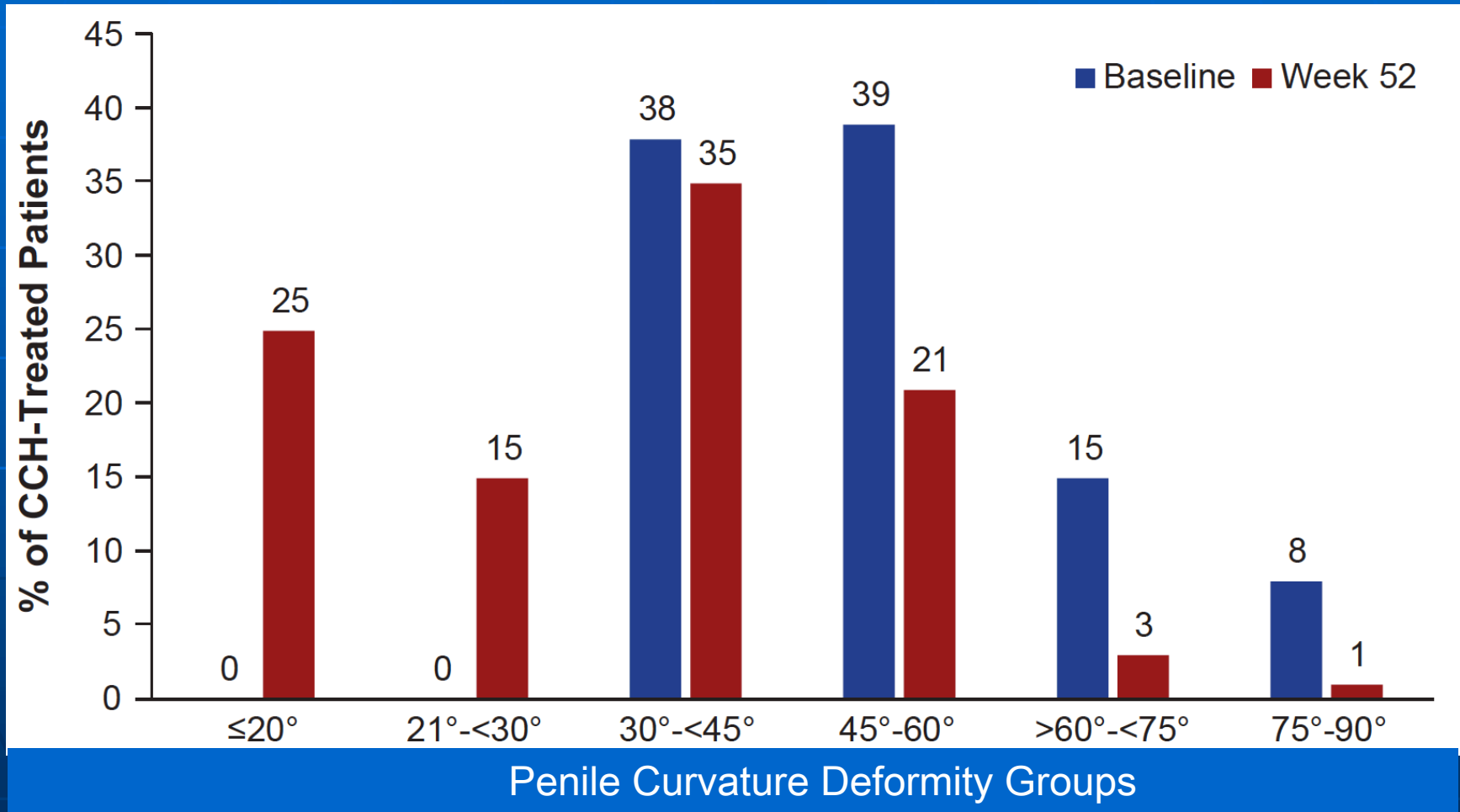




Most Common Adverse Events $\geq 5\%$

	IMPRESS I			IMPRESS II	
	XIAFLEX	Placebo		XIAFLEX	Placebo
	N = 277 n (%)	N = 140 n (%)		N = 274 n (%)	N = 141 n (%)
Penile edema	45 (16.2)	1 (0.7)		40 (14.6)	0 (0.0)
Injection site swelling	30 (10.8)	0(0.0)		35 (12.8)	2 (1.4)
Contusion	28 (10.1)	0 (0.0)		27 (9.9)	1 (0.7)
Ecchymosis	26 (9.4)	0 (0.0)		12 (4.4)	0 (0.0)
Blood blister	9 (3.2)	0 (0.0)		17 (6.2)	0 (0.0)
Injection site hemorrhage	15 (5.4)	10 (7.1)		10 (3.6)	3 (2.1)
XIAFLEX Treatment Related SAEs					
Hematoma	2 (0.7)	0 (0.0)		1 (0.4)	0 (0.0)
Corporal Rupture (penile fracture)	1 (0.4)	0 (0.0)		2 (0.7)	0 (0.0)

Subgroup analysis for the change in penile deformity after CCH therapy.



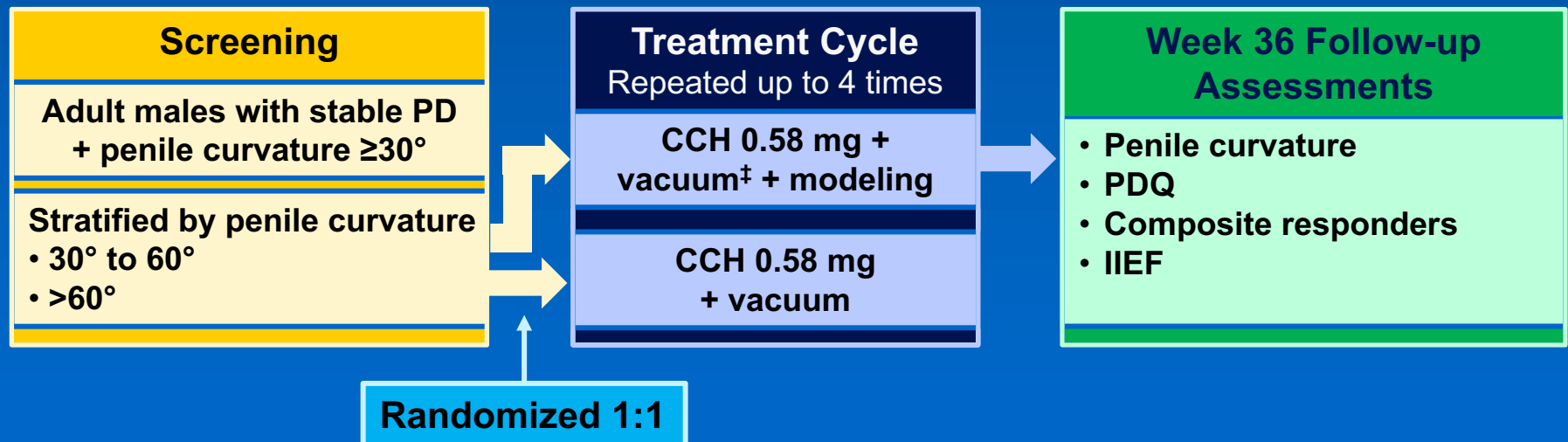
Vacuum therapy in Peyronie's Disease



- N = 31
- 12 weeks x 10mins bd
- Improvement in curvature in 21 men (5 – 25 degrees)
- Raheem et al BJUI 2010

Study Design

- Phase 3b, open-label, pilot study of CCH + vacuum therapy (\pm investigator modeling)*



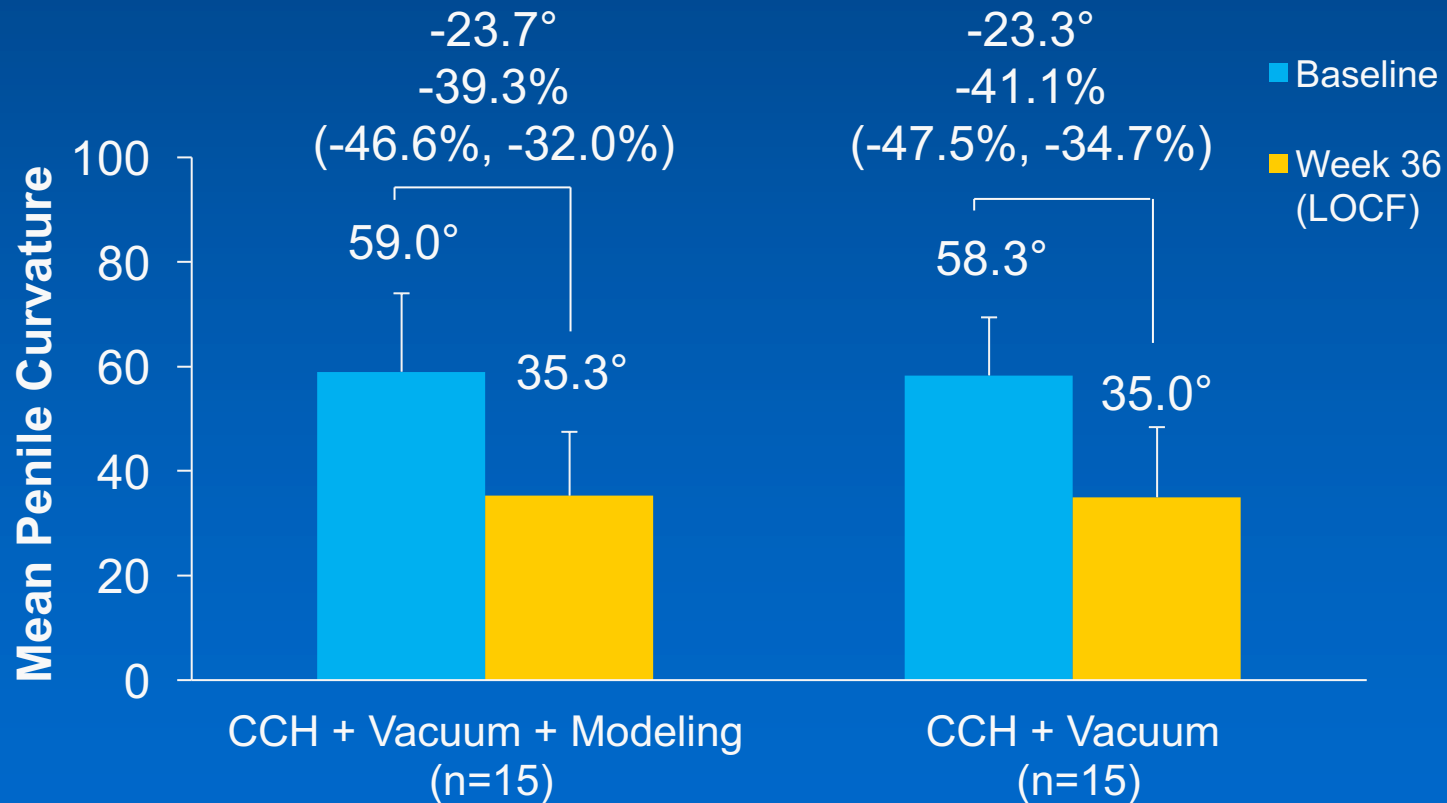
*The efficacy of CCH in combination with vacuum therapy is investigational.

1. Nehra A, et al. *J Urol*. 2015;194(3):745-753. 2. Bilgutay AN et al. *Curr Sex Health Rep*. 2015;7(2):117-131. 3. Xiaflex[®] [package insert]. Malvern, PA: Auxilium Pharmaceuticals, LLC; 2016. 4. Raheem AA et al. *BJU Int*. 2010;106(8):1178-1180.

Patient Population

Parameter	CCH + Vacuum + Modeling (n=15)	CCH + Vacuum (n=15)
Mean age, y (range)	57.8 (38-70)	57.6 (43-74)
Race, n (%)		
White	15 (100.0)	14 (93.3)
Asian	0	1 (6.7)
Baseline number of penile plaques, n (%)		
1	12 (80.0)	14 (93.3)
2	2 (13.3)	1 (6.7)
>2	1 (6.7)	0
Patients with erectile dysfunction, n (%)	6 (40.0)	5 (33.3)
Patients with penile trauma, n (%)	4 (26.7)	3 (20.0)

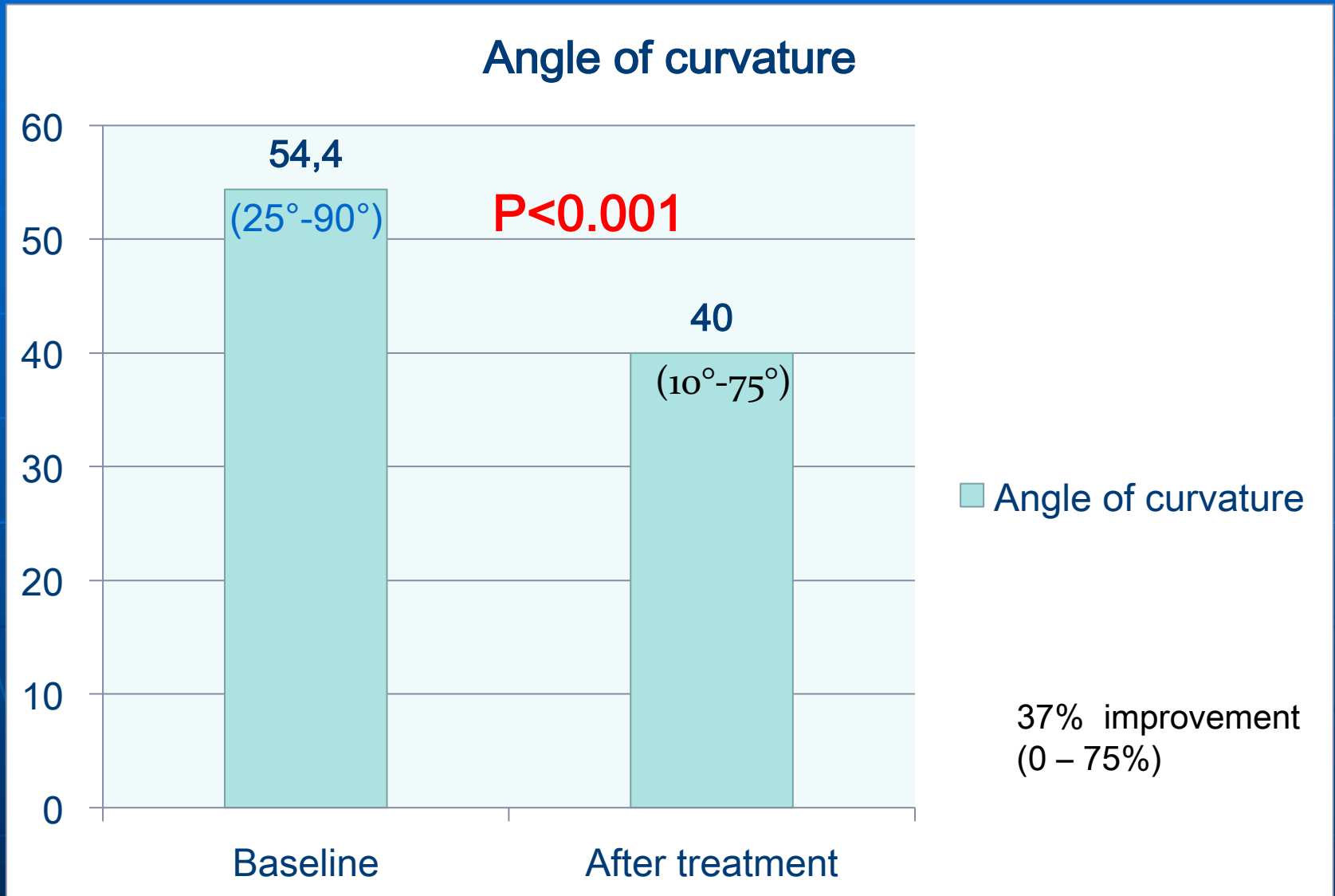
Change From Baseline in Penile Curvature



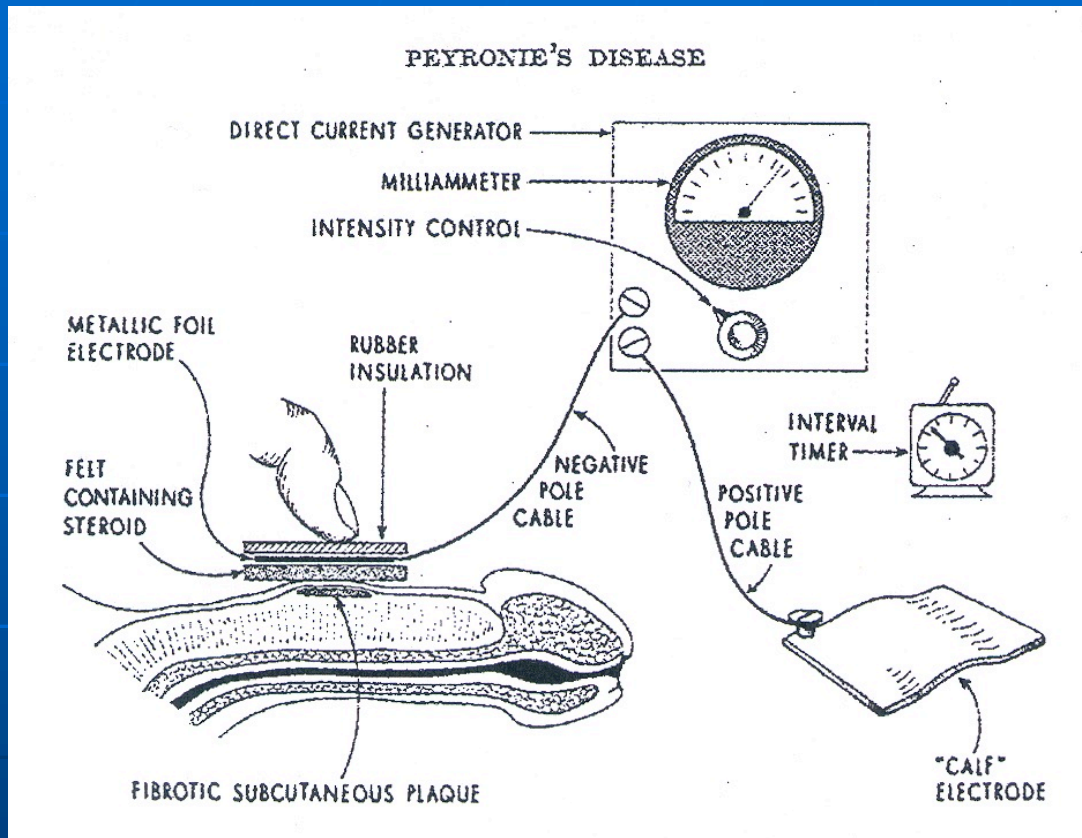
Protocol of injection

- Stable disease
- Ultrasound – mark curvature apex and ? Calcification
- Monthly injection Xiapex
- Home modelling only
- Vacuum 20 minutes/day
- Stop when reached maximum response

Curvature improvement



Iontophoresis



Active transport of ionised molecules

Enhanced drug transport into the plaque

Histamine
Hydrocortisone

Whalen
Rothfield and Murray

J Urol 83, 851, 1960
J Urol 97, 874 1967

Verapamil vs Saline EMDA

2x week for 3 months

	Verapamil	Saline
N	23	19
Curvature improved	15 (9 deg)	11 (7.6 deg)
Improved > 20 degrees	7	4
No change	5	7
Curvature worse	3	1

p = NS

Greenfield ,Levine J Urol 2007; 177:972

Penile Extender



Traction Therapy in Acute Peyronie's Disease

- Non randomised placebo controlled
- Pain/progression, <12mths duration, 6 hrs/day
- 55 traction vs 41 controls for 6/12

Improvement	Traction	Controls	p
n	55	41	
Curvature	20 °	-23 °	p <0.05
VAS	3	-0.5	p <0.05
SPL	1.5cm	-2.6cm	p <0.05
IIEF-EF	+10	-6	p <0.05
SEP 2	42%	-12%	p <0.05

Traction Therapy in Acute Peyronie's Disease

Predictors of success

- Curvature < 45°
- Pain
- Duration < 3/12
- Age < 45yrs
- Plaque volume
- Compliance

ESWT in Peyronie's Disease

	ESWT	Sham
n	16	20
Curvature improvement	- 0.9°	5.3°
IIEF-EF	0.56	0.1
SPL	-0.1cm	0.1cm
VAS change	1	0.8

All p = NS

Low Intensity Extracorporeal Shockwave Therapy (LiESWT)

- Open label, single site, n=30, Duolith SDi ultra
- **Improvements in curvature (>15 degrees in 33%), plaque hardness in 60% and penile pain (4 out of 6 men) following LiESWT**
- There was a moderate improvement in IIEF-5 score (>5 points reported in 20% of men)

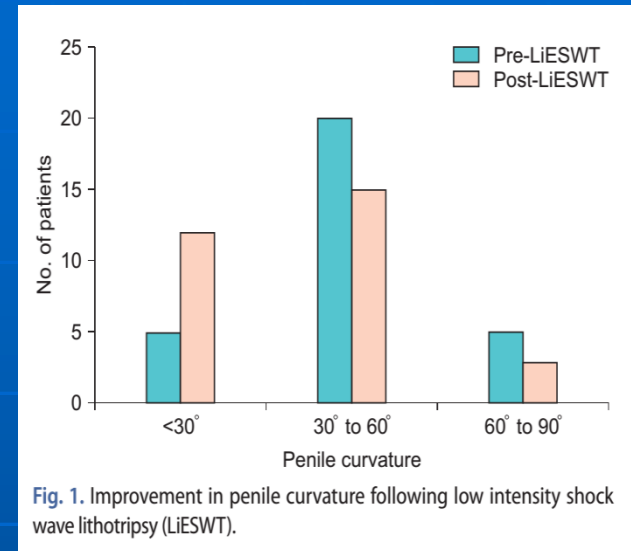


Table 3. Selected published studies on the clinical outcomes of LiESWT in PD

Source	No. of penile curvature reduction/total No. (%)	No. of plaque size reduction/total No. (%)	No. of pain reduction/total No. (%)	No. of sexual function improvement/total No. (%)
Hatzichristodoulou et al. [7]	16/50 (32)	18/50 (36)	17/20 (85)	7/13 (54)
Chitale et al. [8]	3/16 (19)	4/16 (25)	Unknown	Unknown
Palmieri et al. [9]	Unknown	Unknown	23/43 (53)	29/41 (70)
Mirone et al. [10]	260/380 (68)	Unknown	312/340 (92)	303/380 (80)
Abdel-Salam et al. [14]	14/24 (58)	14/24 (58)	17/24 (72)	14/24 (58)
Hauck et al. [15]	2/20 (10)	10/20 (50)	5/9 (56)	3/20 (15)
Husain et al. [16]	Unknown	15/32 (47)	12/20 (60)	Unknown
Lebret et al. [17]	23/54 (43)	59/51 (54)	31/34 (91)	6/24 (25)
Present study	10/30 (33)	8/30 (27)	4/6 (67)	6/10 (60)

LiESWT, low intensity shock wave lithotripsy; PD, Peyronie's disease.

Recommendations ICSM

- **Oral therapy-** There is no evidence of benefit from placebo-controlled trials.
Grade B-Level 2.
- **Intralesional Therapy** Some benefit has been shown
 - Collagenase - Grade B Level 2
 - Interferon Grade B Level 3
 - Verapamil Grade C Level 3
- **Topical Treatment** Topical Verapamil gel is not recommended.
Grade B-Level 3.
Iontophoresis is not recommended.
Grade B, Level 3
- **Shock Wave Therapy** ESWT is not recommended for PD related deformity
Grade B-Level 2
LiESWT – no recommendation Grade B Level 3
- **Traction therapy** May have some benefit Grade C Level 3