Peyronie’s Disease: What to Do & What are the Outcomes?

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Peyronie’s Disease
Prevalence

• **US Study:**
  - 388.6/100,000 (0.4%)
  - Age at onset (ave) 53 years (range 19-83)

• **German Study**
  - 4432 men answered questionnaire
  - Mean age 57.4 years
  - 3.2% with plaque (1% plaque, pain, curve)
  - 30-39 yo 1.5%
  - 40-59 yo 3.0%
  - 60-69 yo 4.0%
  - >70 yo 6.5%
  - 84% curve; 46% painful erection; 40% ED

• **Prostate Cancer Screening**
  - 8.9% of 534 men with palpable plaque
  - Mean age 68.2 vs 61.8 without PD
  - Higher incidence of DM and HT

Emotional Impact of Peyronie’s

- Depression: 48% (21% severe) of men with Peyronie’s. Associated with single man, penile shortening (Nelson et al JSM 2008)

- Emotional problems in 82%. Relationship issues (OR 8.0) and penile length (OR 2.7) independent predictors. (J. Smith JSM 2008)
Testosterone & Peyronies Disease

• 74% of PD patients with TT<300
  – 121 Peyronies patients
  – Lower TT correlated with >curvature
• Lower TT in men with PD with or without ED
• Low T same in PD & ED patients

1. Moreno & Morgantaler JSM 2009;
2. Kehra et al AUA 2008,
Peyronie’s Disease
Delamination Injury

Devine, 1990
Peyronie’s Disease
Pathogenesis

- Penile trauma separating tunical layers
- Fibrin deposits recruit inflammatory cells
- Inflammatory cells (Mast cells & macrophages) release ROS, cytokines & growth factors activating tunical myofibroblasts
- Trapping the inflammatory process with aberrant healing, excessive fibrosis & fragmentation of elastic fibers
- ↑ collagen formation and deposition
- Osteo chondritic transformation

• DISORDERED WOUND HEALING
Peyronie’s Disease

Normal Tunica

Peyronie’s plaque

Collagen I / GAPDH Ratio

***p<0.0001

Ferrini et al Nitric Oxide 6:283-94, 2002
Peyronie’s Genetics

• Array genomic hybridization
• NELL1 deletion in 2/14 (14.4%) men with PD & Duypuytren’s
  – Mutation affecting NELL1 function in 12/14 (86%)
  – Only found in 0.015% in population
  – Gene on chromosome 11
  – Involved in osteogenesis and inflammatory disorders
  – Deletion also seen in Chron’s & ankylosing spondilysis.

L. Lipschultz AAGUS 2015
Peyronie’s Disease
Symptoms

- Penile pain
- Penile plaque
- Curvature on erection
- Erectile Dysfunction
- Paget’s Disease of bone (3%)
- Duypuytren’s contracture (10%)
- Ledderhose disease

Inflammation
Fibrosis
Peyronie’s Disease
Diagnosis

• History: Trauma, family history
• PE: Plaque in penis
• Studies:
  – Ultrasound for plaque calcification
  – Curve evaluation: ICI test, vacuum device
  – Vascular assessment: Color duplex ultrasound
  – DICC if venous leak possibility
Peyronie’s Disease
Vascular Abnormalities

- Doppler Duplex Ultrasound
  - 36% of Peyronie’s with ED are abnormal

- DICC
  - 59% with ED have significant venous incompetence

Lopez & Jarow, 1993
Peyronie’s Disease
Natural history

• Gradual spontaneous resolution
• 97 men with Peyronie’s of 1-5 years
  – 14% resolving
  – 40% progressive
  – 47% not changing
  Gelbard, M. Urol. 1994
• Poor prognosis
  – Duration >2 years
  – Duypuytren’s contracture
  – Plaque calcification
  – Curve >45°
  Lue, T J. Urol 2001
Oral Therapy

Very few well controlled & designed trials

- Vitamin E- RCT No benefit vs placebo (Pryor 1983)
- Potaba® - RCT No benefit (↓ size) vs placebo (Weidner et al 2005)
- Colchicine – No benefit vs placebo (Safarinejad et al 2004)
- Tamoxifen – RCT No benefit vs placebo (Teloken et al 1999)
- L-Carnitine - Better than Tamoxifen (Biagiotti et al 2001)
- Pentoxifylline – RCT improved curve and ED (Safarinejad, BJUi 2010)
- L-Arginine – No controlled data
- Omega 3 – Controlled trial with no benefit (Safarinejad, JSM 2009)
- CoEnzyme Q10 – RCT with benefit for curve and pain (Safarinejad, JSM 2010)
- PDE5 inhibitors– in vivo studies show reduction of penile fibrosis in animal models.
  - Clinical trial in Germany with tadalafil daily shows early promise (Porst, EAU 2014)
Injection Therapy

- **Steroids** – No benefit in uncontrolled studies; Risks – tissue atrophy, ↑ surgical difficulty
- **Verapamil** – ↓ fibroblast proliferation, ↓ ECM production (in vitro). Many studies, most not controlled. Measured improvement in ~60%. Low toxicity.
Collagenase clostridium histolyticum

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

- **FDA approval December 2013**
In Studies 1 and 2, injections consisted of 0.25 mL of:

- Sucrose in a buffer solution
- 0.58 mg of CCH

Approximately 6 weeks

UP TO 4 TREATMENT CYCLES MAY BE ADMINISTERED

1ST In-office injection
1 to 3 days

2ND In-office injection
1 to 3 days

In-office penile modeling procedure

Patient at-home daily penile modeling activities

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>XIAFLEX n=277</td>
<td>Placebo n=140</td>
</tr>
<tr>
<td></td>
<td>CCH</td>
<td>CCH</td>
</tr>
<tr>
<td>Age, y Mean (SD)</td>
<td>57.9 (8.2)</td>
<td>58.2 (8.9)</td>
</tr>
<tr>
<td>Penile curvature deformity, degrees</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>48.8 (30–90)</td>
<td>49.0 (30–89)</td>
</tr>
<tr>
<td>Min–max</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDQ Symptom Bother score (range: 0–16), meana,b</td>
<td>7.5</td>
<td>7.4</td>
</tr>
<tr>
<td>History of erectile dysfunction, n (%)</td>
<td>128 (46.2)</td>
<td>75 (53.6)</td>
</tr>
<tr>
<td>History of penile trauma, n (%)</td>
<td>66 (23.8)</td>
<td>33 (23.6)</td>
</tr>
<tr>
<td>Mean duration of PD, y</td>
<td>3.9</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**PDQ Bother scores did not directly correlate with degree of curvature deformity**

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*a* Each PDQ assessment required subjects to have had vaginal intercourse in the 3 months prior to completion.

*b* Higher scores represent worse symptoms.

Change in Penile Curvature Deformity in Clinical Studies

- Mean baseline measurements of penile curvature deformity were
  - Study 1: **CCH** 48.8°; placebo 49.0°
  - Study 2: **CCH** 51.3°; placebo 49.6°
- Change in penile curvature deformity was similar when stratified by degree of baseline curvature deformity (30° to 60° or 61° to 90°)

![Mean percent change in penile curvature deformity from baseline to week 52*†](image)

**Study 1**
P<0.01†

**Study 2**
P<0.01†

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean Percent Change</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCH</td>
<td>35.0%</td>
<td>199</td>
</tr>
<tr>
<td>Placebo</td>
<td>17.8%</td>
<td>104</td>
</tr>
<tr>
<td>CCH</td>
<td>33.2%</td>
<td>202</td>
</tr>
<tr>
<td>Placebo</td>
<td>21.8%</td>
<td>107</td>
</tr>
</tbody>
</table>

The efficacy population (modified intent-to-treat) comprised a total of 612 intent-to-treat subjects who had both a curvature deformity measurement and a PDQ assessment at baseline and at least one subsequent time point.

*Last observation carried forward (LOCF).*

†Patients were given up to 4 treatment cycles of **CCH** placebo at weeks 0, 6, 12, 18.

‡P values based on an analysis of variance (ANOVA) with factors for drug, stratum of baseline curvature deformity, and their interaction.
Mean Percent Change in Penile Curvature Deformity From Baseline to Week 52: Study 1

- CCH: n=199
- Placebo: n=104

-17.8% P<0.01*
-35.0%

*P value based on an ANOVA with factors for drug, stratum of baseline curvature deformity, and their interaction.
P value based on an LOCF analysis at week 52.
Significantly Reduced Patient-Reported Bother Associated With PD

Mean Change in Patient-Reported Bother

<table>
<thead>
<tr>
<th>Domain Score at week 52</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CCH</td>
<td>CCH</td>
</tr>
<tr>
<td></td>
<td>n=199</td>
<td>n=202</td>
</tr>
<tr>
<td>Mean change from baseline expressed as % of mean baseline</td>
<td>-37.3%</td>
<td>-35.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td>n=104</td>
<td>Placebo</td>
</tr>
<tr>
<td>Mean change</td>
<td>-1.6</td>
<td>-1.5</td>
</tr>
<tr>
<td>n=104</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Baseline scores: Study 1: CCH -7.5; Placebo -7.4; Study 2: CCH 7.4; Placebo -8.2
- Patient-Reported Bother score range: 0-16 (higher numbers represent greater bother)
## Studies 1 and 2: Adverse Reactions

Adverse Reactions (≥1% of CCH Treated Subjects and at a Greater Incidence Than Placebo) After up to 4 Treatment Cycles

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XIAFLEX N=551, %</th>
<th>Placebo N=281, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse reactions</td>
<td>84.2</td>
<td>36.3</td>
</tr>
<tr>
<td>Penile hematoma(^a)</td>
<td>65.5</td>
<td>19.2</td>
</tr>
<tr>
<td>Penile swelling(^b)</td>
<td>55.0</td>
<td>3.2</td>
</tr>
<tr>
<td>Penile pain(^c)</td>
<td>45.4</td>
<td>9.3</td>
</tr>
<tr>
<td>Penile ecchymoses(^d)</td>
<td>14.5</td>
<td>6.8</td>
</tr>
<tr>
<td>Blood blister</td>
<td>4.5</td>
<td>0</td>
</tr>
<tr>
<td>Penile blister</td>
<td>3.3</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus genital</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>Painful erection</td>
<td>2.9</td>
<td>0</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>1.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

\(^a\)Includes: injection site hematoma and penile hematoma were reported with the verbatim term of penile bruising or injection site bruising in 87% of subjects;  
\(^b\)Includes: injection site swelling, penile edema, penile swelling, local swelling, scrotal swelling, and injection site edema;  
\(^c\)Includes: injection site pain, penile pain, and injection site discomfort;  
\(^d\)Includes: contusion, ecchymoses, penile hemorrhage, and injection site hemorrhage.

Carson et al, EAU 2014
Assessment of Meaningful Change

- The GAPD was used to establish subject-perceived response to treatment
  - Would you say that the symptoms and effects of Peyronie’s disease are:
    - Much worse
    - Moderately worse
    - A little worse
    - About the same, hardly any change
    - Improved in a small but important way
    - Moderately improved
    - Much improved

- Subjects were grouped and examined according to their penile curvature at Week 52 as a defined clinical endpoint
  - Groups: \( \leq 20^\circ, 21^\circ - <30^\circ, 30^\circ - <45^\circ, 45^\circ - 60^\circ, >60^\circ - <75^\circ, 75^\circ - 90^\circ \)
Results

Percentage of Subjects Within Penile Curvature Deformity Groups at Week 52\textsuperscript{a}

- **At baseline**
  - 77% of subjects were $\leq 60^\circ$
  - 38% were $\geq 30^\circ$ to $< 45^\circ$
  - 23% were $> 60^\circ$ to $\leq 90^\circ$

- **At week 52**
  - 75% of subjects were $< 45^\circ$
  - 25% of subjects were $\leq 20^\circ$

\textsuperscript{a}Last observation carried forward
Results (cont.)

Mean GAPD at Week 52

<table>
<thead>
<tr>
<th>Degrees of Penile Curvature</th>
<th>Mean GAPD at Week 52</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤20°</td>
<td>2.4</td>
</tr>
<tr>
<td>21°-&lt;30°</td>
<td>1.5</td>
</tr>
<tr>
<td>30°-&lt;45°</td>
<td>1.1</td>
</tr>
<tr>
<td>45°-60°</td>
<td>0.4</td>
</tr>
<tr>
<td>&gt;60°-&lt;75°</td>
<td>0.3</td>
</tr>
<tr>
<td>75°-90°</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Penile Curvature Deformity Groups at Week 52

- Mean Baseline Penile Curvature
- Mean Week 52 Penile Curvature
- Range of Penile Curvature at Baseline

Mean Percent Reduction in Curvature

- 69.8%
- 42.7%
- 25.5%
- 11.1%
- -3.5%
- -6.5%
Conclusions

• The groups with mean reductions in penile curvature ≥25.5% had mean GAPD scores ≥1
  – This suggests that, in these groups, PD symptoms and effects improved in a small but important way, moderately improved, or much improved

• 75% of men reported a meaningful change in symptoms and effects of PD on their life following CCH treatment that resulted in 25.5% or greater improvement in penile curvature deformity
Shock Wave Therapy- Controlled Trial

• Prospective, randomized, placebo-controlled, single blind study
• 102 men with stable PD
• Eval- Pain VAS. Curvature with erection before & 6 wk after Tx
• 2000 shocks q wk x 6 with active ESWL vs. placebo (plastic membrane interposed)
• Results-
  – ↓ pain in treatment arm –
  – no change in deformity overall.
• Conclusion: ESWT can not be recommended for treatment of curvature

Hatzichristodoulou et al Eur Urol 2008
SWL & Peyronie’s Disease

- 100 men with < 12 mo PD
- DBPCR Trial
- 2000 shocks to plaque
- F/U at 12 & 24 Weeks
- Statistically signif ↓ pain, curvature & ED

A Palmeiri et al Eur Urol 2009
Peyronie’s Disease
Criteria for Surgery

• Disease duration > 12 months
• Stable plaque & curve > 3 months
• Difficulty with coitus
  – Patient pain or difficult intromission
  – Partner discomfort
  – Inadequate erection
    • Hour glass deformity
    • Poor rigidity or duration
Peyronie’s Disease
Selection of Surgical Technique

• Plication (Nesbit Procedure)
  – Moderate curvature
  – No hour glass deformity
  – Potent +/- pharmacologic therapy

• Incision/excision + graft (Horton-Devine)
  – Short penis
  – Significant curve >60°
  – Potent +/- Pharmacologic therapy
  – Hour glass deformity
Complications of Plication Surgery

- Objective loss of penile length 18–41%
- Subjective loss of penile length 50–75%
- Loss of penile length affecting intercourse 5–11.9%
- Recurrent curvature requiring reoperation 0–20%
- Worse erectile dysfunction 0–6%
- Change in penile sensation 6–75%
- Palpable suture knots (using nonabsorbable suture) 50–100%
- Sutures interfering with intercourse 0–10%

Graft Material for Peyronie’s Disease

- Dermis
- Vein (saphenous, deep dorsal)
- Tunica vaginalis
- Cadaveric pericardium
- SIS
- Temporalis fascia
- Rectus fascia
- Lyophylized dura mater
- Pedicaleed preputial flap
Post Op Rehabilitation

- Daily extender or VED for 12 weeks
- Daily tadalafil 5 mg for 12 weeks
- Resume coitus at 6 weeks
- On demand PDE 5i
Penile Traction Therapy

- 74 men completed 12 IVIs
- PTT 2–8 hours daily; no longer than 2 hr/session.
- Stretched penile length (SPL) and erect penile curvature (EPC)
- Response defined >10º ↓ in EPC.
- 35 group I vs. 39 PTT group II completed the protocol. 54% PTT responded vs. 46% in group I (P = 0.75).
- Responders in group II had a mean EPC improvement of 26.9 degrees vs. 20.9 degrees in group I (P = 0.22).
- Mean PTT 3.3 hr/day
  - men with >3 hours per day use gained 0.6 cm in SPL vs. 0.07 cm using less than or equal to 3 hours per day (P = 0.09).
  - men in group I lost 0.74 cm of SPL on average.

**Multivariate analysis**: duration of PTT use predicts length gain (0.38 cm gain for every additional hour per day of PTT use, P = 0.007).

Peyronie’s Disease
Grafting Problems

• Continued curve
  – Inadequate correction
  – Recurrence
  – Graft contracture

• Sensory loss or persistent pain

• Erectile dysfunction

• Penile Shortening

• Graft aneurysm/bulging

• Hour-glass deformity
### Plaque Incision & Grafting

**Risk of Post Operative ED**

Multivariate analysis of 62 men

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>OR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curve &gt;60°</td>
<td>3.0</td>
<td>1.9-4.8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Curve &gt;45° &lt;60°</td>
<td>1.2</td>
<td>0.8-2.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pre op PDE5i</td>
<td>4.2</td>
<td>2.1-12.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Age &gt; 55</td>
<td>4.1</td>
<td>1.9-8.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Venous leak</td>
<td>12.4</td>
<td>8.2-22.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre op Verapamil</td>
<td>1.1</td>
<td>0.5-2.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

Lentz et al SMSNA 2011
Selection of Surgical Technique

• Penile Implant
  – Inadequate erections with pharmacological therapy
  – Patient preference
  – Failure of other technique
**Peyronie’s Disease**

**Modeling & IPP**

<table>
<thead>
<tr>
<th>Prosthesis</th>
<th>Pt</th>
<th>Straight (%)</th>
<th>Plaque Incision (%)</th>
<th>Complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson &amp; Delk</td>
<td>AMS 700CX</td>
<td>138</td>
<td>118(86)</td>
<td>11(8)</td>
</tr>
<tr>
<td>Montague</td>
<td>AMS 700CX</td>
<td>34</td>
<td>34(100)</td>
<td>0(0)</td>
</tr>
<tr>
<td></td>
<td>AMS 700 Ultrex</td>
<td>38</td>
<td>28(74)</td>
<td>10(26)</td>
</tr>
<tr>
<td>Carson</td>
<td>AMS 700CX</td>
<td>30</td>
<td>28(93)</td>
<td>2(7)0(0)</td>
</tr>
</tbody>
</table>
Full distraction (sliding) of the corporal bodies

The tunica albuginea is incised to the level of the corpus cavernosum, using needle tip bovie set at 20 watts. Initially, the proximal dorsal semicircular incision is created.

Corpus spongiosum

Dorsal neurovascular bundle

The remaining tunica incisions are then created for full distraction (sliding) of the corporal bodies.
Peyronie’s Disease & IPP

Conclusions

• Semi rigid rod prosthesis have poor patient & partner satisfaction (Montorsi, 1993)

• 3 piece inflatable implant & penile modeling effective in straightening with minimal morbidity

• IPP & Peyronie’s similar morbidity, function & satisfaction to men without Peyronie’s