Peyronie’s Disease Pharmacotherapy and Traction Therapy

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Presenting Symptoms and Duration\textsuperscript{1-4}

- Curvature – 80-91%
- Nodule – 15%
- Pain – 3-22%
- ED – 15-28%
- Penile shortening – 14%

\begin{itemize}
  \item <1 mo
  \item 1-3 mo
  \item 4-6 mo
  \item 7-12 mo
  \item Chronic >12 mo
  \item 12-24 mo
  \item >24 mo
\end{itemize}
Acute Phase Natural History

Natural History – Early vs Late Presentation

≤ 2 years

≥ 4 years

Pain and curvature may continue to improve

*Not statistically significant

An Aside

• Important to discuss MR Safarinejad
• 5 important RCTs on PD therapies from MR Safarinejad
• 42 RCTs since 2001; 22 single author
• Publications withdrawn due to questionable validity
• Cochrane review noted significant discrepancies in his data compared to similar cohorts
• Data to be reported at face value
Pharmacologic and Traction Therapies Reviewed

- **Oral**
  - Vitamin E
  - Potassium Para-aminobenzoate (Potaba)
  - Tamoxifen
  - Colchicine
  - Carnitine
  - PDE5 Inhibitors
  - Pentoxifylline
  - Omega-3 fatty acids
  - Coenzyme Q10

- **Topical**
  - Verapamil
  - Trifluoperazine
  - Magnesium Sulfate
  - Liposomal Superoxide Dismutase

- **Topical + Iontophoresis**
  - Verapamil
  - Dexamethasone
  - Lidocaine

- **Penile traction and vacuum erection devices**

***Only reviewing RCT data (penile traction / VED exempt)***
Oral Therapies
Vitamin E (Tocopherol)

- **Mechanism:**
  - Antioxidant / free radical scavenger
  - Reducing penile fibrosis
- **Adverse events**
  - High doses (>400 IU/day) increases serious events (stroke, MI, ?prostate ca)
  - GI symptoms
- **Benefits**
  - Inexpensive
  - Readily available

![Chemical structure of Vitamin E](image-url)
Vitamin E vs Carnitine vs Placebo

Safarinejad, et al.¹
- RCT, PC
- PD 12-42 mo

6 mo treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Curve (%)</th>
<th>Pain (%)</th>
<th>Plaque (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18.4%</td>
<td>60.0%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Carnitine</td>
<td>20.4%</td>
<td>63.0%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Vit E + Carnitine</td>
<td>22.6%</td>
<td>62.3%</td>
<td>13.2%</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>18.9%</td>
<td>60.4%</td>
<td>11.3%</td>
</tr>
</tbody>
</table>

Results* (C=Curve, P=Pain, Plq=Plaque)

*P=0.09 (curve), 0.1 (pain), 0.1 (plaque)

Vitamin E vs Intralesional Interferon

Inal, et al.\textsuperscript{1}

- RCT
- PD x 10.8 months

Results* (C=Curve, P=Pain, Plq=Plaque)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Curve</th>
<th>Pain</th>
<th>Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILI IFN x 12 wks</td>
<td>C -1.5°</td>
<td>P 71%</td>
<td>Plq +0.02</td>
</tr>
<tr>
<td>Vit E 400IU bid x 6 mo</td>
<td>C +1.5°</td>
<td>P 50%</td>
<td>Plq +0.13</td>
</tr>
<tr>
<td>ILI IFN + Vit E</td>
<td>C -1.5°</td>
<td>P 83.3%</td>
<td>Plq -0.08</td>
</tr>
</tbody>
</table>

*P > 0.05 for all parameters

\textsuperscript{1} Inal T, et al: 2006 Urology.
Vitamin E + Colchicine vs Ibuprofen

Prieto Castro, et al.¹

- RCT
- PD < 6 mo
- Deformity < 30°
- Treatment x 6 mo

N=45

Ibuprofen 400mg qday

- Curve Imp 18%*
- Pain Imp 68%
- Plaque +0.13*

Vit E 600mg qday + Colchicine 1g q12h

- Curve Imp 48%*
- Pain Imp 91%
- Plaque -0.26*

*P=0.01 and 0.001, respectively

Vitamin E vs Sildenafil

Ozturk, et al.\(^1\)

- RCT

\(N=39\)

12 wks treatment

\(\text{Pain} 42.8\%^*\)
\(\text{Plaque} -33.3\%\)

\(\text{Pain} 66.6\%^*\)
\(\text{Plaque} -33.3\%\)

\(*P=0.045\)

**Take Home**

- No evidence for benefit in chronic phase
- Limited data suggesting benefit when combined with colchicine in acute phase
- Inferior to sildenafil on improving pain

Potassium Para-aminobenzoate (Potaba)

- **Mechanism:**
  - Anti-inflammatory
  - Stabilization of serotonin-monoamine oxidase activity (anti-fibrotic)
- **Adverse events**
  - GI upset
  - Skin photosensitization
- **Other**
  - Expensive - $375/month
Potassium Para-aminobenzoate (Potaba)

- Multicenter, RCT, PC\(^1\)
- N=75, PD < 12 mo
- Potaba 3g/qid x 12 mo
- Response:
  - Decrease plaque
  - Decrease curve \(\geq 30\%\)
- Dropout:
  - Potaba (14%)
  - Placebo (8%)
- Pain improvement similar
- Pts with no baseline curvature developed less curve with Potaba

Take Home

- Early in disease course, Potaba may prevent further worsening of disease
- No improvement of established curvature

Tamoxifen

- **Mechanism:**
  - Estrogen receptor antagonist
  - Modulates the release of TGF-β1
  - Blocks TGF-β receptors
  - Confirmed antifibrotic activity in retroperitoneal fibrosis

- **Adverse events:**
  - Nausea, muscle cramps, sensory paresthesias, changes in libido

- **Other:**
  - Inexpensive

Tamoxifen

- RCT, PC¹
- N=25, mean 20 mo duration
- Consecutive patients
- All with plaque, no hourglass
- Tamoxifen 20mg bid x 3 mo
- Similar rate of AE (8%)
  - Gastritis

Tamoxifen vs Acetyl-L-carnitine

- RCT\(^1\)
- N=48, acute=15
- Tamoxifen 20mg bid vs Carnitine 1g bid
- Treatment - 3 mo
- Evaluated up to 6 mo
- Curve improved in carnitine
- Plaque size improved in both

\(P < 0.01\)

ILI Verapamil + Carnitine vs ILI Verapamil + Tamoxifen

- RCT\(^1\)
- N=60, chronic disease (mean 13 mo)
- Verapamil 10mg weekly x 10 wk
- Propionyl-L-carnitine 2g/day x 3 mo
- Tamoxifen 40mg/day x 3 mo


**Take Home**

Among men with chronic PD:
- Tamoxifen does not improve curvature
- Likely does not impact plaque volume
- Inadequate data in acute phase
- Inferior to carnitine
Colchicine

- Mechanism:
  - Down-regulates TGF-B expression
  - Inhibits tubulin movement
  - Reduces leukocyte action / diminishes wound contracture
- Adverse events:
  - GI, neutropenia, anemia, bone marrow suppression
- Other
  - Most common choice by American urologists
  - ~$500 / month
Vitamin E + Colchicine vs Ibuprofen

Prieto Castro, et al.  
- RCT  
- PD < 6 mo  
- Deformity < 30°  
- Treatment x 6 mo

N=45  

Ibuprofen 400mg qday  
- Curve Imp 18%*  
- Pain Imp 68%  
- Plaque +0.13*

Vit E 600mg qday + Colchicine 1g q12h  
- Curve Imp 48%*  
- Pain Imp 91%  
- Plaque -0.26*

*P=0.01 and 0.001, respectively

Colchicine vs Placebo

- RCT, PC, n=78\(^1\)
- Mean disease 15 mo
- Colchicine 0.5-2.5 mg qday x 4 mo

\[ \text{Pain Resolution} \]
\[ \text{Curvature Improvement} \]
\[ \text{Change in Plaque Vol} \]

\[ \text{P = } >0.05 \]

**Take Home**

**In acute phase**
- May improve curvature / pain when combined with Vitamin E

**In chronic phase**
- No evidence for benefit

<table>
<thead>
<tr>
<th></th>
<th>Colchicine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>60%</td>
<td>64%</td>
</tr>
<tr>
<td>Curvature</td>
<td>-1º</td>
<td>+3º</td>
</tr>
<tr>
<td>Plaque Vol</td>
<td>+0.11</td>
<td>+0.11</td>
</tr>
</tbody>
</table>

\(^1\) – Safarinejad MR: 2004 IJIR.
Carnitine

• Mechanism:
  • Antiproliferative effect on endothelial cells
• Sources
  • Red meat / dairy
• Adverse events
  • GI, Seizures, “fishy odor”
• Other
  • Inexpensive
Safarinejad, et al. ¹

- RCT, PC
- PD 12-42 mo

6 mo treatment

Results* (C=Curve, P=Pain, Plq=Plaque)

Vit E vs Carnitine vs Placebo

N=236

Vit E 300mg bid

Carnitine 1g bid

Vit E + Carnitine

Placebo

C 18.9%
P 60.4%
Plq 11.3%

C 20.4%
P 63%
Plq 12.9%

C 22.6%
P 62.3%
Plq 13.2%

C 18.4%
P 59.2%
Plq 11.1%

*P=0.09 (curve), 0.1 (pain), 0.1 (plaque)

ILI Verapamil + Carnitine vs ILI Verapamil + Tamoxifen

- RCT\(^1\)
- N=60, chronic phase (mean 13 mo)
- Verapamil 10mg weekly x 10 wk
- Propionyl-L-carnitine 2g/day x 3 mo
- Tamoxifen 40mg/day x 3 mo

Tamoxifen vs Acetyl-L-carnitine

• RCT¹
• N=48, acute=15
• Tamoxifen 20mg bid vs Carnitine 1g bid
• Treatment - 3 mo
• Evaluated up to 6 mo
• Curve improved in carnitine
• Plaque size improved in both

Take Home

• Two types of carnitine evaluated
  • Propionyl-L-carnitine
  • Acetyl-L-carnitine
• Mixed data on benefits of propionyl
• Limited data showing benefit of acetyl over tamoxifen on curvature and plaque size

PDE5 Inhibitors

- **Mechanism:**
  - Antifibrotic (cGMP and NO)
  - Secondarily inhibits TGF-β1
- **Adverse events:**
  - Flushing, congestion, Headache
- **Other**
  - Cost
  - Secondary benefits on erectile function
ESWT vs ESWT + Tadalafil

- RCT, ED+PD\(^1\)
- Inclusion:
  - PD ≤ 12 mo
  - Curve <30
  - Painful erections

\[ \text{N}=100 \]

\[ \text{ESWT + tadalafil 5mg qday} \]
\[ \text{ESWT alone} \]

\[ \text{4 wks} \]
\[ \text{12 and 24 wks*} \]

- Curve -1\(^\circ\)
  - Pain 74%
  - Plaque -0.06 to 0.09cm\(^2\)

- Curve -1\(^\circ\)
  - Pain 80%
  - Plaque -0.05cm\(^2\)

* \(P>0.05\); Pain = painful erections

Vitamin E vs Sildenafil

Ozturk, et al.\textsuperscript{1}

- RCT

N=39

Vitamin E 400 IU qday

Sildenafil 50 mg qday

\textsuperscript{*}P=0.045

Pain 42.8%*

Plaque -33.3%

Pain 66.6%*

Plaque -33.3%

12 wks treatment

Take Home

- No evidence for benefit of PDE5s on curvature / plaque
- Possible improvement in penile pain

Pentoxifylline

• Mechanism:
  • Nonselective PDE inhibitor
  • Anti-inflammatory
  • Inhibits fibroblast proliferation
  • Downregulates TGF-B
  • Increases fibrinolytic activity
• Adverse events:
  • GI, dizziness, headache, flushing
• Other:
  • Inexpensive
**Pentoxifylline vs Placebo**

- **RCT, PC, 6 mo, n=228**
- **Inclusion:**
  - > 12 mo, pain during erection, able to penetrate, plaque < 2cm (non-painful, non-calcified plaque), PD+ED, progression on other oral therapies

### Pain with Erection Curvature (Δ% change)

<table>
<thead>
<tr>
<th></th>
<th>Plaque Area (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pentoxifylline</strong></td>
<td></td>
</tr>
<tr>
<td>400 mg bid</td>
<td>-89%</td>
</tr>
<tr>
<td>Dorsal</td>
<td>-22%</td>
</tr>
<tr>
<td>Lateral</td>
<td>-20%</td>
</tr>
<tr>
<td>Ventral</td>
<td>-40%</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>400 mg bid</td>
<td>-83%</td>
</tr>
<tr>
<td>Dorsal</td>
<td>+31%</td>
</tr>
<tr>
<td>Lateral</td>
<td>+22%</td>
</tr>
<tr>
<td>Ventral</td>
<td>+27%</td>
</tr>
<tr>
<td><strong>P =</strong></td>
<td>0.07</td>
</tr>
<tr>
<td>0.001 to 0.01</td>
<td></td>
</tr>
</tbody>
</table>

**Take Home**

- Single trial demonstrates efficacy of pentoxifylline in all parameters in chronic PD refractory to other oral agents

1 – Safarinejad MR: 2004 IJIR.
**Omega-3 Fatty Acids**

- **Mechanism:**
  - Stimulates production of collagenase
- **Dietary Sources (EPA / DHA):**
  - Fish / marine sources, select dairy products
- **Adverse events:**
  - GI, “Fishy” odor
- **Other:**
  - Inexpensive
Omega-3 vs Placebo

- RCT, DB, PC
- Mean PD duration ? 16-22 mo
- Mean curve ~30°
- Eicosapentaenoic + docosahexaenoic acids 1.84g/day

Inclusion:
- Pain during erection
- Able to penetrate
- Non-painful scar
- Plaque <2cm², non-painful
- Failed prior oral therapy

N=224

Take Home

- Omega-3 fatty acids (EPA+ DHA) are not effective in chronic phase PD patients refractory to other oral PD therapies

*P > 0.05 for all variables
Coenzyme Q10

- **Mechanism:**
  - Antioxidant
- **Dietary Sources:**
  - Beef, chicken, pork, fish
- **Adverse events:**
  - Increased risk of bleeding, pruritus, rash, GI
- **Other:**
  - Inexpensive
Coenzyme Q10 vs Placebo

- RCT, DB, PC\(^1\)
- Mean PD duration 20 mo
- Mean curve \(\sim 30-35^\circ\)
- CoQ10 300mg qday

Inclusion:
- ED+PD
- Pain during erection
- Able to penetrate
- Non-painful scar,
- Plaque <2cm\(^2\), non-painful
- Failed 2 prior oral therapies

*\(P < 0.001\) for curve, plaque, > 0.05 for pain

Take Home

- Limited data suggests CoQ10 improves curve and plaque size in chronic phase PD refractory to other oral agents

N=186
Liposomal Superoxide Dismutase vs Placebo

- SOD – Free radical scavenger
- RCT, PC, DB\(^1\)
- Crossover, 8 wk
- N=39

Assessments:
- Baseline, 4, 8, 12 wks

Patients:
- 23% with prior PD therapies
- 79% with curvature
- Pain improvement primary endpoint

\(P=0.017\), \(P=0.015\)

Verapamil vs Trifluoperazine vs MgSO4 vs Placebo

- RCT, PC, DB
- 3 mo tx, then open label verapamil x 6 mo
- Mean duration 3.4 yr, curve 45°
- Objective measures:
  - Pt estimate of curvature
  - Pain = yes/no
  - Plaque by calipers

Topical Ver vs TriF vs MgSO4 vs Placebo

*P = <0.05; Ver vs Plc

How Much Verapamil is Actually Absorbed in the Penile Plaque?

- Martin, et al\textsuperscript{1}:
  - N=8, ED undergoing IPP
  - 1 week prior to surgery, verapamil administered peri-urethrally at penoscrotal junction x 1 hour
  - Applied 10 PM night before and 5 AM morning of surgery
  - Strip of corpora taken
  - Chromatography

- Verapamil noted in urine but not in tunical samples

Topical Therapies

**Adverse Effects:**
- **Topical verapamil**
  - 11% contact dermatitis
- **Trifluoperazine**
  - 71% (anxiety, agitation, blurred vision, insomnia, depression)
- **Dexamethasone**
  - Skin thinning, discoloration

**Other**
- **Cost**

**Take Home**
- Limited data suggests a benefit for topical verapamil
- Findings are questionable due to a lack of evidence demonstrating tunical absorption
Topical + Iontophoresis Therapies
# Topical Therapies – Iontophoresis

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>N=</th>
<th>Type</th>
<th>Rx</th>
<th>Δ Pain</th>
<th>Δ Curve</th>
<th>Δ Plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehrsai (2013)</td>
<td>60</td>
<td>RCT Ver + Dex</td>
<td>TEA -4.1/10</td>
<td>ILI -1.8/10</td>
<td>&lt;30º at end</td>
<td>TEA 87%ILI 67%</td>
</tr>
<tr>
<td>Greenfield (2007)</td>
<td>42</td>
<td>DB, PC Ver vs Saline Rx</td>
<td>65% (-9º) Sal 58% (-8º)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Di Stasi (2004)</td>
<td>73</td>
<td>Ver + Dex (Rx) vs Lido (Con)</td>
<td>No Pain: Rx 76% Con 11%</td>
<td>*Rx -22º</td>
<td>*Rx -496mm³</td>
<td>*Rx -5mm³</td>
</tr>
<tr>
<td>Montorsi (2000)</td>
<td>25</td>
<td></td>
<td>Ver + Dex</td>
<td>Rx -100%</td>
<td>Rx -88%</td>
<td>Rx -90%</td>
</tr>
<tr>
<td>Montorsi (2000)</td>
<td>40</td>
<td>RCT, DB, PC</td>
<td>Orgotein + Dex + Lido</td>
<td>*Rx -100% PC -12%</td>
<td>*Rx 62% Imp PC 5% Imp</td>
<td>*Rx -79% PC -5%</td>
</tr>
</tbody>
</table>

**Take Home**

- Iontophoresis with verapamil and dexamethasone likely improves pain, curvature, and plaque volume over placebo
- Data are limited

* = Significance
Traction and Vacuum Therapies
# Traction and Vacuum Therapy in PD

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Type</th>
<th>Rx</th>
<th>Δ IIEF EFD</th>
<th>Δ Pain</th>
<th>Δ Curve</th>
<th>Length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Martinez-Salamanca (2014)</td>
<td>96</td>
<td>Retro; 1º Tx</td>
<td>PTT x 6 mo (6-8 hr/day)</td>
<td>*PTT +6 Con -6</td>
<td>*PTT -3 Con +2.4</td>
<td>*PTT -20º Con +22º</td>
<td>*PTT +1.5 Con -2.4</td>
</tr>
<tr>
<td>Rybak (2012)</td>
<td>111</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gontero (2009)</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTT +1.3</td>
</tr>
<tr>
<td>Levine (2008)</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PTT +0.5 to 2.5</td>
</tr>
<tr>
<td>Raheem (2010)</td>
<td>31</td>
<td>Tx</td>
<td>bid x 3 mo</td>
<td></td>
<td>-5 to -20º</td>
<td></td>
<td>35% with +0.5 to +1.5</td>
</tr>
<tr>
<td>Lue (1999)</td>
<td>4</td>
<td>Retro; Surg</td>
<td>VED daily x 6 mo (up to 18 mo)</td>
<td></td>
<td></td>
<td>+2.5 to +10 (combined surgical lengthening)</td>
<td></td>
</tr>
</tbody>
</table>

**Take Home**

- PTT as primary and/or adjunctive therapy may improve length, curvature, pain, and erectile function
- VED with inadequate data in PD
Summary

1. No consistent, strong evidence to definitively suggest efficacy and/or superiority of any one oral therapy in PD

2. Oral therapies with limited evidence suggesting a benefit on curve / plaque
   - Colchicine + Vit E – Acute phase
   - Potaba – Acute phase
   - Acetyl carnitine
   - Pentoxifylline – Chronic phase
   - CoQ10 – Chronic phase

3. Oral therapies with no proven benefits on curve / plaque
   - Tamoxifen
   - PDE5 Inhibitors
   - Omega-3 fatty acids
Summary

4. Topical therapies
   - Superoxide dismutase may improve pain
   - Verapamil may improve curve / plaque – mechanism unclear
   - Iontophoresis with verapamil + dexamethasone likely improves curvature, pain, and plaque volume

5. Penile traction therapy improves length, and may improve curvature, pain, and erectile function

6. Insufficient data on vacuum therapies in PD
Thank you