Peyronie’s Disease

Gerald H. Jordan, MD
Department of Urology
Eastern Virginia Medical School
Norfolk, VA
Peyronie’s disease is a scarring phenomenon affecting the tunica albuginea of the penis. Scar tissue forms “plaques” that can result in pain with erection, penile curvature/deviation, penile shortening, indentations, and/or erectile dysfunction. Histological staining shows fibrin accumulation and excessive depolarized collagen deposition. It is associated with difficulty with sexual intercourse, loss of self-esteem, and depression. There are no approved therapies for the treatment of Peyronie’s disease.

Peyronie’s Disease in History

- FALLOPIUS -- 1561
- de la PEYRONIE -- 1743

INDURATIO PLASTICA PENE
Peyronie’s Disease In History
Peyronie’s Disease

- Incurable
- Reassurance
- Medical Therapy
- Surgery
Peyronie’s Disease

Fibrous Lesions - Impede Expansion

- Curvature And / Or
- Indentation And / Or
- Foreshortening
Peyronie’s Disease Update
Incidence of Peyronie’s Disease

- Beta Blockers
- Phenytoin
- Paget’s Disease
- Diabetes Mellitus
Incidence of Peyronie’s Disease

- Familial
  - Dupuytren’s 15 - 30 %
  - 10 - 40 %
- Autosomal Dominant

Nyberg. JU, 1982; Ralph. JU, 1997
Incidence of Peyronie’s Disease

- 1 - 100
- Age of Onset - 53yrs (MEAN)
- Prevalence - 0.4 %
- Rheu Arth, Hypertension
- Asymptomatic Prevalence: 22 / 100

Incidence of Peyronie’s Disease

- 45 - 65 Years
  - PEAK MID 50’s
- Loss Of Tissue Elasticity
- Erectile Dysfunction
Causes of Peyronie’s Disease

- Trauma - Insertion Septum
- Localized Aberration Wound Healing
- Associated With ED
- Associated Fibrin Deposition

Etiology - Trauma

- Midline Septal Insertion - Vulnerable with Buckling

Etiology - Genetics

- Paget’s Disease Of The Bone
- Dupuytren's Contracture
- Certain HLA Subtypes
- Autoimmune Disease
- Hyperactive Wound Healing

Pathology

- Round Cell Infiltration
- Obliterated Space of Smith
- Fibrin Deposits

Pathology –
Round Cell Infiltration; Obliterated Space of Smith

Pathology

- Dense Collagen
- Decreased Elastin
- Dystrophic Calcification
- Cartilaginous Metaplasia

Anatomy - Tunica Albuginea

- Multilayered
- 1.5 - 3.0 mm thick
- Incompetent Septum
- Longitudinal Layer
  - Thinnest 3 - 9 O’clock

Anatomy - Tunica Albuginea

- Dorsal Opposite Ventral - Upward Bending
- Septum Joins Circ Layer - Delamination

Anatomy - Tunica Albuginea

- Plaque Usually Dorsal

Anatomy - Tunica Albuginea

- Compliance of the Tunica
- Collagen is Brittle
- Elastin Stretches
- Helical Arrangement Straightens
- Elastin Stretches
- Ground Substance Displaces
Peyronie’s Disease Update

Figure 5.3: A collagen fibril (a) displays periodic banding with a distance (D) of 68 nm between repeating bands. It is made up of staggered collagen molecules (b), each of which is about 300 nm long and 15 nm in diameter (c). The collagen molecule consists of a triple helix (d), the three components of the triple helix consist of alpha chains. Each third amino acid of the alpha chain is a glycine. The X portion following glycine is frequently a proline, and the Y position preceding the glycine is frequently a hydroxyproline (e). (Based on Frisco DJ, Guzmon NA. Hospital Practice 12:2, Dec. 1977.)
Molecular Basis of Injury

- Repeated Mechanical Stress - Microvascular Trauma
- Delamination
- Bleeding
- Fibrinogen

Molecular Basis of Injury

- Pain And Inflammation
- Vasoactive Factors
- Is The Inflammatory Response “Trapped?”
- PDGF-A and PDGF-B, TGF-b1

Molecular Basis of Injury

- Wound Healing
  - TGF-b1

- Implicated in Soft Tissue Fibrosis
- Implicated in ED
- Increases Synthesis of Fibroblasts –
- Fibrosis
- Causes Increased Connective Tissue
- Inhibits Collagenases
- Can Induce It’s Own Production

Disease Progression

- **Active Phase**
  - Painful Erections – Sometimes Changing Deformity

- **Secondary Phase**
  - Pain Resolves
  - Stable Deformity

Psychological Aspects

- Poorly Defined in the Literature
- Mentioned Only In Passing

Psychological Aspects

- Disturbed Body Image
- Fearful Of Treatment
- Many Functional Aspects of ED
- Like “Death”
  - Denial
  - Ambivalence
  - Anxiety
  - Depression
  - Shame
  - Embarrassment
  - Self Disgust

Psychological Aspects

- Youthful Libido
- Aging Tissues
- Relate With Intercourse
- Do Not “Like” To Talk About the Problem

Psychological Aspects

Most Patients:

- Told “End Of Sex Life”
- Admit … Are Coping Poorly
- Believe “Sex Is Intercourse”
- Must Be Told To Keep “Sexual Expression Alive”

Jones. AUA Update, 1998
Clinical Features

- Plaque or Induration:
  - Usually Located Dorsal Septal Insertion
  - Can Be Multiple
  - Can Involve Septal Fibers
  - Patients May Not Be Aware

Clinical Features

Penile Pain:

- Usually Only With Erection
- Usually Not Severe But Can Interfere With Intercourse
- Spontaneous Improvement The Rule As Inflammation Resolves

Clinical Features

Curvature and/or Deformity:

- Usually Dorsal Curve
- Curvature Can Be Complex
- Lateral or Ventral – Disabling
- Can Cause Indentation

Clinical Features
Clinical Features

Erectile Dysfunction:

- Reported Incidence - Variable

Clinical Features

- Reduced Elastin - Increased Type III Collagen
- Associated with Veno-occlusive Problems
- Cavernosal Fibrosis Can Interfere with Arterial Flow

Medical Management - Oral

- Vitamin E (tocopherol) – antioxidant
- Potaba (Para Aminobenzoate)
- Allegra (Seldane)
- Colchicine
- Tamoxifen
- Carnitine (Acetyl-L-Carnitine/Propionyl-L-Carnitine)
- Trental (Pentoxifylline)
- Natulan (Procarbazine)
- Steroids or NSAIDs
- PDE-5 Inhibitors
Medical Management - Oral

- Rigorous Well Designed / Controlled Studies Are Needed

- As It Stands Now, The Role Of Oral Therapy To Alter The Progress Of Peyronie's Disease Is Probably Limited To The Acute Phase Of Disease

Mynderse And Monga, I J Imp Res, 2002
Medical Management – Intralesional Injection

- Steroids
- Parathyroid Hormone
- Orgotein
- Verapamil
- Interferon α-2b
Medical Management - Topicals

- Steroids, Verapamil, Beta – Aminopropionitrile, Orgotein
  - Transcutaneous Absorption of Drug
  - No Blinded / Controlled Studies
  - No Proven Efficacy - Single Reports Only
Medical Management –
Iontophoresis / Electromotive Therapy

- Steroids, Verapamil, Orgotein, Histamine
  - Enhanced Transcutaneous Absorption Of Drug Using Surface Delivered Heat Or Current
  - No Blinded / Controlled Studies
  - No Proven Efficacy - Single Reports Only
Non-Surgical Management

- **Lithotripsy**
  - Questionable Rationale - Ostensibly Mechanical Disruption of the Plaque Enhancing Compliance
  - No Blinded / Controlled Studies
  - No Proven Efficacy To Date, ? Ill Effects on the Erectile Tissue, ? Adjuvant to Intralesional Injection

Medical Management - Combined Therapy

- **Intralesional Injection And Oral**
  - Interferon $\alpha$-2b + Vit E
  - Verapamil + Carnitine
  - Verapamil + Tamoxifen
- **Oral Vit E + Colchicine**
- **Lithotripsy + Intralesional Verapamil**
  - Birmingham Study Underway
- **Ved + Intralesional Verapamil**
  - Study Protocol Under Evaluation

Investigations Suggest That Part Of The Peyronie’s Process Involves Suppression Of “Antifibrotics”

- Matrixmetalloproteinases
- α1 Antitrypsin
- Cyclic GMP

Surgical Management Indications

- When The Deformity Precludes Intercourse
- Erectile Dysfunction Precludes Intercourse
Surgical Management Pre-operative Assessment

- Stable / Quiescent Disease
- Usually > 1yr from onset of symptoms
- Stable deformity for 3 – 5 Mos
- Pain Free
- Detailed Assessment of Erectile Function
- CDU
- DICC
- True Informed Consent
Surgical Management Options

- Plication Or Tunical Resection
  - Tunical Resection With Plicating Closure

- Corporoplasty

Surgical Management Options

- Plication Or Tunical Resection
Surgical Management Options

- Excision / Incision With Grafting
Surgical Management Options
Surgical Management Options

Prosthetic Implantation With Straightening

Medical Management – XIAFLEX

- Clostridial Collagenase (XIAFLEX)
  - Creation of “Chemical Incisions” with Initiation of Remodeling
  - Blinded / Controlled Studies Underway
  - Available Only on Protocol

Safety and Efficacy of Injectable Mixed Collagenase Subtypes (XIAFLEX) in the Treatment of Peyronie’s Disease
Objectives

- To assess the impact of injectable mixed collagenase subtypes (XIAFLEX, Auxilium) on the angle of penile deviation and plaque size.

- To assess the tolerability and safety of XIAFLEX for the treatment of Peyronie’s disease.
Methods: Study Design

Study A (N=25)

- Baseline
  - ≤3 injections (7–10 d)
    - Week 12
  - Month 6 Follow-up

Study B (N=10)

- Baseline
  - ≤3 injections (5–10 d)
    - Week 6
    - Week 12
  - Month 6 Follow-up
  - Month 9 Follow-up
Methods: Patients

Key inclusion criteria:
- Men aged 18–75 years
- Diagnosis of Peyronie’s disease

Key exclusion criteria:
- Prior surgery for Peyronie’s disease
- Extensively calcified plaque
- Substantial erectile deficits due to Peyronie’s disease
- Penile bend <20 degrees
- Sexual dysfunction due to other causes
Assessment of Efficacy and Tolerability

Study A:
- **Primary**: changes from baseline in the angle of deviation and plaque size
- **Secondary**: patient responses on VAS for pain and sexual function
- **Secondary**: investigators’ global evaluation of change

Study B:
- **Primary**: patients’ responses on the Peyronie’s Patient Questionnaire at month 9
- **Secondary**: changes from baseline in angle of deviation and plaque size
- **Secondary**: investigators’ global evaluation of change

- **Tolerability**: adverse events monitored in both studies
<table>
<thead>
<tr>
<th>Study</th>
<th>Enrollment</th>
<th>Disposition</th>
<th>Demographics</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study A:</strong></td>
<td>25 men enrolled and 18 completed the study</td>
<td>Mean age was 55 years; 92% were white</td>
<td>Mean duration of illness was 39 months</td>
<td></td>
</tr>
<tr>
<td><strong>Study B:</strong></td>
<td>10 men enrolled; 9 completed the study</td>
<td>Mean age was 58 years; 90% were white</td>
<td>Mean duration of illness was 32 months</td>
<td></td>
</tr>
</tbody>
</table>
Results: Clinical Success,* Deviation Angle

*Clinical success: ≥25% reduction in the angle of deviation.
Results: Clinical Success,* Plaque Size

*Clinical success: ≥25% reduction in plaque size.

Study A

<table>
<thead>
<tr>
<th></th>
<th>M3</th>
<th>M6</th>
<th>M9</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>95</td>
<td>65</td>
<td>67</td>
</tr>
</tbody>
</table>

*Clinical success: ≥25% reduction in plaque size.
## Results: Mean Change From Baseline in Deviation Angle and Plaque Size

<table>
<thead>
<tr>
<th></th>
<th>Deviation Angle (°)</th>
<th>Plaque Length (cm)</th>
<th>Plaque Width (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study A</td>
<td>Study B</td>
<td>Study A</td>
</tr>
<tr>
<td>Baseline</td>
<td>52.8</td>
<td>50.2</td>
<td>5.8</td>
</tr>
<tr>
<td>W6</td>
<td>NA</td>
<td>−15.2*</td>
<td>NA</td>
</tr>
<tr>
<td>M3</td>
<td>−12.7*</td>
<td>−20.6†</td>
<td>−0.94†</td>
</tr>
<tr>
<td>M6</td>
<td>−11.1†</td>
<td>−28.4†</td>
<td>−0.48‡</td>
</tr>
<tr>
<td>M9</td>
<td>−6.6</td>
<td>−26.2‡</td>
<td>−0.68</td>
</tr>
</tbody>
</table>

* $P \leq 0.007$ versus baseline.  
† $P \leq 0.001$ versus baseline.  
‡ $P \leq 0.05$ versus baseline.
Results: Peyronie’s Patient Questionnaire (Study B)

- Patient-reported improvements in sexual function were observed for:
  - Enjoyment of intercourse ($P=0.023$)
  - Satisfaction with sexual relationships ($P=0.043$)
  - Freedom from pain during erection ($P=0.009$)

- At baseline, 4 patients reported no sexual activity, and at month 9, 100% (9/9) were sexually active

- All 9 patients reported pain-free erections
Results: Physical Symptoms (Study B)

- Pain with erection: resolved in 6 patients
- Plaque palpability: disappeared in 4 patients with moderate-to-severe palpation
- Penile indentation: disappeared in 3 patients and improved from severe to moderate in 1 patient
- Penile shortening: improved from severe to moderate in 1 patient
- Penile numbness: moderate-to-severe completely resolved in 1 patient
Results: Investigators’ Global Assessment of Patients Much Improved/Very Much Improved

Study A

- M3: 59%
- M6: 53%
- M9: 56%

Study B

- W6: 50%
- M3: 67%
- M6: 67%
- M9: 67%
## Adverse Events: Study A

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Relationship to Study Drug, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Possibly</td>
</tr>
<tr>
<td>Reproductive system</td>
<td></td>
</tr>
<tr>
<td>Erectile disturbance</td>
<td></td>
</tr>
<tr>
<td>Penile disorder NOS</td>
<td></td>
</tr>
<tr>
<td>Penile pain</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Penile swelling</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Contusions</td>
<td></td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

NOS = not otherwise specified.
# Adverse Events: Study B

<table>
<thead>
<tr>
<th>Treatment-Related Adverse Event, n (%)</th>
<th>Total (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>5 (50)</td>
</tr>
<tr>
<td>Local swelling</td>
<td>2 (20)</td>
</tr>
<tr>
<td>Suprapubic pain</td>
<td>4 (40)</td>
</tr>
<tr>
<td>Injury, poisoning, and procedural pain</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Contusion</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>9 (90)</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Painful erection</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Penile pain</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Penile swelling</td>
<td>7 (70)</td>
</tr>
<tr>
<td>Penis disorder</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Hematoma</td>
<td>1 (10)</td>
</tr>
</tbody>
</table>
The most common treatment-related adverse events were localized administration site reactions of mild intensity and of limited duration (typically within 3 weeks).

The most common adverse events were contusion, penile pain, and ecchymosis.

All adverse events resolved without medical intervention.
Conclusions

- XIAFLEX, administered in up to 3 series of multiple injections, appears to be effective for the treatment of Peyronie’s disease

- Treatment with XIAFLEX was generally well tolerated

- Larger controlled clinical trials are needed to confirm these promising results and are in the process of development
Peyronie’s Disease

Gerald H. Jordan, MD
Department of Urology
Eastern Virginia Medical School
Norfolk, VA