Rehabilitation of Erectile Function

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Australian Centre for Sexual Health
St. Leonards, Sydney
Sexual Dysfunction Post RP

- **Erectile Dysfunction**
- Anejaculation
- Anorgasmia
- Dysorgasmia (painful ejaculation)
- Climaturia (orgasm associated urine leak)
- Loss of penile length
- Penile curvature
Post-RP ED

- ED associated with reduced HRQOL
- ED source of concern & regret for patients
# Sexual Function & Bother

<table>
<thead>
<tr>
<th>Level of sexual function</th>
<th>None, very small or small</th>
<th>Moderate</th>
<th>Great</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good or very good</td>
<td>102 (90%)</td>
<td>8 (7%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Very poor or poor</td>
<td>36 (12%)</td>
<td>30 (10%)</td>
<td>229 (78%)</td>
</tr>
</tbody>
</table>

Litwin et al, 1995
Post RP RD & Depression

### Correlations with HADS Depression Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital Status</td>
<td>0.15</td>
<td>0.01</td>
</tr>
<tr>
<td>Age</td>
<td>0.07</td>
<td>0.17</td>
</tr>
<tr>
<td>Disease Stage</td>
<td>0.03</td>
<td>0.64</td>
</tr>
<tr>
<td>Treatment (RT vs. RP)</td>
<td>-0.16</td>
<td>0.01</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Social Support</td>
<td>-0.43</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Erectile Function</strong></td>
<td>-0.12</td>
<td>0.03</td>
</tr>
</tbody>
</table>

### Multiple regression results predicting HADS depression scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>Beta</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marital Status</td>
<td>-0.05</td>
<td>-1.16</td>
<td>0.25</td>
</tr>
<tr>
<td>Age</td>
<td>0.11</td>
<td>2.24</td>
<td>0.03</td>
</tr>
<tr>
<td>Disease Stage</td>
<td>0.01</td>
<td>0.03</td>
<td>0.98</td>
</tr>
<tr>
<td>Treatment Type</td>
<td>-0.09</td>
<td>-1.17</td>
<td>0.08</td>
</tr>
<tr>
<td>Social Support</td>
<td>-0.20</td>
<td>-4.14</td>
<td>0.001</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.51</td>
<td>10.83</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Erectile Function</strong></td>
<td>-0.10</td>
<td>-2.26</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Post RP ED & Bother

Epidemiology of Post-RP ED

- Large variance in reported incidence of ED
- Medline search 1991-2004 found 436 articles for T1 or T2 N0M0 CaP

Post-RP ED Prevalence Reporting

- Data acquisition methods
- Definition of ED
- Population studied
Minimizing ED Post-RPS

- Nerve sparing surgery
- Artery sparing surgery?
- Intra-operative neurostimulation?
- Cavernous nerve interposition grafting?
- Pharmacologic neuromodulation
- Penile rehabilitation
Recovery of Erections Post RP

• **Definite Predictors**
  – Degree of nerve sparing
  – Pre-operative erectile function
  – Patient age
  – Post-operative penile haemodynamics
  – Surgeon experience & volume
  – Vascular risk factors

• **Non-Predictors**
  – Tumour volume
  – Pre-operative PSA
  – Surgical margin status
Recovery of Erections

Patient Age

Pre-Op Erectile Function

Extent of Nerve Sparing

**Penile Rehabilitation**

- **Definition:** Penile rehabilitation is defined as the use of any drug or device to maximize erectile function recovery.

- **Purpose:** The prevention of smooth muscle and endothelial structural alterations to maximize chances of a man returning to his preoperative erectile function level.

- **Candidates:**
  - Radical Pelvic Surgery
  - Pelvic radiation
  - Diabetes Mellitus
  - Pelvic Fracture
ISSM 2009 Recommendation
Grade C

• Given the strong animal and basic science evidence and understanding the strengths and weaknesses of the existing human studies and the negative consequences of long-term ED after RP, the committee suggests that penile rehabilitation has significant potential benefits for the patient/partner and should be considered after RP.
Post RP ED Pathophysiology

- Endothelial Damage
- Neural Injury
- Smooth Muscle Damage
Post-RP ED Mechanisms

- **Neurogenic**
  - Cavernous nerve interruption/cautery
  - Cavernous nerve traction or exposure
  - Anatomic vs functional integrity

- **Neural trauma leads to structural alterations**
  - Cavernosal hypoxia
  - Apoptosis
  - Up-regulation of fibrogenic cytokines
  - Excess collagen production

- **Structural changes lead to venous leak**

Cavernosal Oxygenation

**Flaccid Penis**

\[ pO_2 = 35-40 \text{ mm.Hg} \]

↑ TGF-\( \beta_1 \) secretion

↑ Collagen Production

 Corporal Fibrosis & Venous Leak

**Erection**

\[ pO_2 = 70-100 \text{ mm.Hg} \]

↑ PGE secretion

↓ Collagen Production

Preservation of Erectile Tissue

cAMP Production in Varied Oxygen States
Systemic Hypoxia Reduces Erection Hardness

- 21% FiO₂
- 20% FiO₂
- 19% FiO₂
- 18% FiO₂

ICP, mmHg & Flow, ml/min

Nerve stim

ICP reduced

Intracavernosal pressure (ICP)

Pudendal artery inflow

Wayman C et al. ESSM 2005 Poster P 01-153
The Effect of Hyperbaric Oxygen Therapy on Erectile Function Recovery in a Rat Cavernous Nerve Injury Model

Incidence of arterial insufficiency remained stable throughout 4 time groups, while incidence of venous leakage increased with time postoperatively (p=0.01)

Patients with post-RP venous leakage were less likely to regain functional erections (p=0.01)
Cross Sectional Anatomy

- Tunica albuginea
- Subtunical venule
- Smooth muscle
CCSM and Venous Leakage

CCSM Alterations After RP

Pre-Op

2/12 Post RP

Elastic and collagen fibers in 19 patients before, and 2 and 12 months after radical prostatectomy

<table>
<thead>
<tr>
<th>Mean Fibers ± SD</th>
<th>Elastic/High Power Field</th>
<th>Collagen/% Biopsy Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>129.32 ± 13.13</td>
<td>44.80 ± 5.73</td>
</tr>
<tr>
<td>After 2 mos</td>
<td>80.80 ± 23.26</td>
<td>55.05 ± 5.29</td>
</tr>
<tr>
<td>After 12 mos</td>
<td>44.20 ± 11.58</td>
<td>73.10 ± 7.85</td>
</tr>
</tbody>
</table>

Before vs after 2 and 12 months, and after 2 vs 12 months p <0.0003.

Iacono F et al. J Urol, 163:1673-76, 2005
Accessory Pudendal Arteries

- Arises from obturator, vesical, femoral, internal iliac a. and terminates in CA
- May be a major source of CA perfusion
- Variable prevalence [1-3]
- Cadaveric study showed that 50% of men have accessory pudendal artery (APA) which terminates in CA (Breza, 1989) [1]

## Accessory Pudendal Arteries

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th># Patients</th>
<th>Incidence (%)</th>
<th>APA Preserved (%)</th>
<th>Study Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matin</td>
<td>2006</td>
<td>70</td>
<td>26</td>
<td>78</td>
<td>LRP</td>
</tr>
<tr>
<td>Secin</td>
<td>2005</td>
<td>325</td>
<td>30</td>
<td>83</td>
<td>LRP</td>
</tr>
<tr>
<td>Rogers</td>
<td>2004</td>
<td>2399</td>
<td>4</td>
<td>100</td>
<td>ORP</td>
</tr>
<tr>
<td>Polascik</td>
<td>1995</td>
<td>835</td>
<td>4</td>
<td>79</td>
<td>ORP</td>
</tr>
<tr>
<td>Droupy</td>
<td>1999</td>
<td>12</td>
<td>75</td>
<td>NR</td>
<td>TRUS</td>
</tr>
<tr>
<td>Rosen</td>
<td>1990</td>
<td>195</td>
<td>7</td>
<td>NR</td>
<td>Angio</td>
</tr>
<tr>
<td>Gray</td>
<td>1982</td>
<td>73</td>
<td>21</td>
<td>NR</td>
<td>Angio</td>
</tr>
<tr>
<td>Benoit</td>
<td>1999</td>
<td>85</td>
<td>70</td>
<td>NR</td>
<td>Cadaver</td>
</tr>
<tr>
<td>Breza</td>
<td>1989</td>
<td>10</td>
<td>70</td>
<td>NR</td>
<td>Cadaver</td>
</tr>
</tbody>
</table>
• 84/2399 (4%) potent men had APA identified at RRP

• APA preservation increased the likelihood of potency, especially in men <60 years, but was not significantly different from control

<table>
<thead>
<tr>
<th>Accessory Artery</th>
<th>Total Patients (n)</th>
<th>Patients Potent (% in Category)</th>
<th>P Value</th>
<th>Median Time to Recover Potency (mo)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral</td>
<td>11</td>
<td>11 (100)</td>
<td>NA</td>
<td>6 (3–18)</td>
<td>0.508†</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>7 (100)</td>
<td></td>
<td>10.5 (3–12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4 (100)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>41</td>
<td>35 (85)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>32 (91)</td>
<td>0.031†</td>
<td>6 (3–24)</td>
<td>0.005†</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>3 (50)</td>
<td></td>
<td>22 (6–48)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42</td>
<td>39 (93)</td>
<td>0.077‡</td>
<td>6 (3–24)</td>
<td>0.009†</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>7 (70)</td>
<td></td>
<td>12 (3–48)</td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td>52</td>
<td>42 (81)</td>
<td>0.110§</td>
<td>9 (3–18)</td>
<td>0.020∥</td>
</tr>
</tbody>
</table>
Animal Data Supporting PDE5i Erectile Rehabilitation

- Muller A et al. The functional and structural consequences of cavernous nerve injury are ameliorated by sildenafil citrate. J Sex Med, 2008; Epub ahead of print

- Kovanecz I et al. Long-term continuous sildenafil treatment ameliorates CVOD induced by cavernosal nerve resection in the rats. IJIR, 2008; 20:202

- Ferrini M et al. Vardenafil prevents fibrosis and loss of smooth muscle after bilateral cavernosal nerve resection in the rat. Urology, 2006; 68:429

- Vignozzi L et al. Effect of chronic tadalafil administration on penile hypoxia induced by cavernous neurotomy in the rat. J Sex Med; 2006; 3:419

- Kovanecz I et al. Chronic daily tadalafil prevents the corporal fibrosis and venocclusive dysfunction that occurs after cavernosal nerve resection. BJUI; 2008; 101:203

- Lysiak JJ et al. Tadalafil increases AKT and extracellular signal-related kinase 1/2 activation and prevents apoptotic cell death in the penis following denervation. J Urol, 2008; 179:779
Clinical Evidence Regarding Rehabilitation

- Rehabilitation strategies have grown over the past decade and include ...
  - Intracavernosal Injections
  - PDE5 inhibitors
  - Intra-urethral Alprostadil
  - Vacuum Therapy
  - Neuromodulatory Agents

- Teloken reported that 84% of urologists (n=301/41 countries) performed some form of penile rehabilitation, including postoperative PDE5i (95%), ICI (75%), vacuum erection device (30%), and intraurethral alprostadil (10% [1])

Current Rehabilitation Strategies

• **PDE5i**
  - Prevention of endothelial structural alterations [1,2]
  - Prevention of smooth muscle structural alterations [3]
  - Preservation of smooth muscle relaxation profile [4]
  - Neuroregeneration [5,6]
  - Erection-independent cavernosal oxygenation? [7]

• **Advantages**
  - Excellent safety profile

• **Disadvantages**
  - Unclear efficacy
  - Cost

7. Ghofrani et al. JACC 2004
Chronic Treatment with Tadalafil Improves Endothelial Function in Men with Increased Cardiovascular Risk

Giuseppe M.C. Rosano\textsuperscript{a,1}, Antonio Aversa\textsuperscript{b,1,*}, Cristiana Vitale\textsuperscript{a}, Andrea Fabbri\textsuperscript{c}, Massimo Fini\textsuperscript{a}, Giovanni Spera\textsuperscript{b}

- Chronic TAD improves endothelial function (FMD) in patients with increased cardiovascular risk regardless their degree of ED
- Benefit is sustained for at least two weeks after TAD discontinuation
PDE5i Increase Stem cells ...

- Recent studies have suggested chronic PDE5i treatment increases generation of endothelial progenitor cells (EPCs) to normal levels in patients with ED [1-4]

Sildenafil Preserves CCSM

- 21 patients (11 in Group 1 and 10 in Group 2) met all inclusion criteria and completed the study

<table>
<thead>
<tr>
<th></th>
<th>Pre-Op</th>
<th>Post-Op</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of CCSM SIL 50 mg</td>
<td>51.5</td>
<td>52.7</td>
<td>NS</td>
</tr>
<tr>
<td>% of CCSM SIL 100 mg</td>
<td>42.8</td>
<td>56.9</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Schwartz et al, J Urol 171:771, 2004
Sildenafil Overcomes Systemic Hypoxia-induced ED

Sildenafil (Viagra) Induces Neurogenesis and Promotes Functional Recovery After Stroke in Rats

Ruilan Zhang, MD; Ying Wang, MD; Li Zhang, MD; Zhenggang Zhang, MD, PhD; Wayne Tsang, BS; Mei Lu, PhD; Lijie Zhang, MD; Michael Chopp, PhD

(Stroke. 2002;33:2675-2680.)

<table>
<thead>
<tr>
<th>Groups</th>
<th>% of Foot-Faults</th>
<th>Before Ischemia</th>
<th>4 d</th>
<th>7 d</th>
<th>14 d</th>
<th>21 d</th>
<th>28 d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil 2 mg/kg, 2 h</td>
<td></td>
<td>1.1±0.01</td>
<td>22.81±3.1</td>
<td>15.2±1.6†</td>
<td>13.2±1.2†</td>
<td>9.1±1.5†</td>
<td>8.2±1.4</td>
</tr>
<tr>
<td>Sildenafil 5 mg/kg, 2 h</td>
<td></td>
<td>1.02±0.02</td>
<td>17.9±2.9</td>
<td>16.6±1.4*</td>
<td>14.6±2.1*</td>
<td>9.5±1.6†</td>
<td>7.6±1.4</td>
</tr>
<tr>
<td>Sildenafil 2 mg/kg, 24 h</td>
<td></td>
<td>1.03±0.03</td>
<td>25.3±3.8</td>
<td>14.4±1.0†</td>
<td>10.0±0.5†</td>
<td>9.0±0.5†</td>
<td>5.3±0.8*</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td>1.06±0.07</td>
<td>31.4±3.4</td>
<td>24.9±3.0</td>
<td>22.0±2.6</td>
<td>19.4±2.7</td>
<td>11.8±1.9</td>
</tr>
</tbody>
</table>
Daily PDE5 Inhibitors

- There are 2 large, prospective, randomized, multi-centre RCTs after bilateral nerve sparing radical retropubic prostatectomy (BNSRRP)
  - Sildenafil [1]
  - Vardenafil (REINVENT) [2]

Randomized, double-blind, placebo-controlled study of postoperative nightly sildenafil citrate for the prevention of erectile dysfunction after bilateral nerve-sparing radical prostatectomy

H Padma-Nathan¹, AR McCullough², LA Levine³, LI Lipshultz⁴, R Siegel⁵,⁹, F Montorsi⁶, F Giuliano⁷ and G Brock⁸, on behalf of the Study Group¹⁰

- RCT 76 post-BNSRRP men - 50-100 mg SIL or placebo for 9/12 with no ICI
- Endpoints - NPT at 1, 4, 8 & 12/12 post-op, successful penetration at 12/12
Results

- Profound loss of NPT at 1/12
- SIL produced 7 fold NPT improvement at 12/12 with most benefit in the first 4/12
- 8/52 post study end, 24% of 50mg and 33% of 100-mg SIL recipients vs. 5% of placebo recipients were responders

Effect of Nightly versus On-Demand Vardenafil on Recovery of Erectile Function in Men Following Bilateral Nerve-Sparing Radical Prostatectomy

Francesco Montorsi\textsuperscript{a,*}, Gerald Brock\textsuperscript{b}, Jay Lee\textsuperscript{c}, JoAnn Shapiro\textsuperscript{d}, Hendrik Van Poppel\textsuperscript{e}, Markus Graefen\textsuperscript{f}, Christian Stief\textsuperscript{g}

- **REINVENT** Study – Complex study design, Bayer Schering sponsor
- A randomised, double-blind, double-dummy, multicentre 13/12 trial comparing nightly VAR, on-demand VAR and placebo in men with pre-op IIEF-EF domain $>25$ (n=628)

REINVENT Study
Primary endpoint was not met...

REINVENT: IIEF-EF domain score ≥22 after 2 months of washout (primary efficacy variable)

No active Treatment!!

Patients previously on:

- Placebo
- Vardenafil nightly
- Vardenafil on-demand

Estimated rate (%)

n=153 n=143 n=149

All between group comparisons non-significant


REINVENT Study
Secondary endpoint

% of subjects with IIEF-EF domain score ≥22 (mild/no ED) after 9 months of double-blind treatment (9/12)

REINVENT Study
Secondary endpoint Results

- On-demand VAR had superior IIEF-EF domain & SEP3 to nightly VAR (p=0.0065)

- The superiority of on-demand therapy is not surprising as the OD arm used VAR for sex, while the Nightly arm used a placebo for sex

REINVENT Study

• Complicated design - Multiple different dosing arms
• 9/12 study period too short
• Primary endpoint – % subjects with IIEF-EF domain score ≥22 (mild/no ED) after 9/12 Rx + 2/12 placebo
• 423 completers/87 centers = ~5 patients/center
• 30% drop-out rate (x2 fold in placebo group)
• Variability in nerve sparing
• No assessment of vardenafil compliance

Possible explanations for stark contrast between **REINVENT** results and the robust data from preclinical animal trials and the sildenafil trial

- **PDE5i plays no role in penile rehabilitation and the animal model is not relevant to humans**

- **Complexity of the trial design obscured any therapeutic effect**
  - Multiple uncontrolled confounders e.g. age, surgeon expertise, pre-op sexual function, nerve sparing status, medical comorbidities, hormonal status, and endothelial function etc

- **Differences in the molecular action of SIL compared with VAR**
  - No head-to-head comparison trial in this population
  - But ... animal studies demonstrate that all have a positive effect on erectile tissue and function preservation
  - On the other hand ... a randomized, controlled trial of all 3 in pulmonary hypertension demonstrates superior pulmonary artery oxygenation with SIL compared to VAR [2]

- **Incorrect VAR dosing**
  - Doses of vardenafil used in pulmonary hypertension are 10–15 mgs 2–3 times per day

Current Rehabilitation Strategies

- **Intracavernosal injection therapy**
  - Cavernosal oxygenation
  - Penile stretch

- **Advantages**
  - Effective erectogenic therapy after RP
  - Cost

- **Disadvantages**
  - Unclear efficacy [1,2]
  - Invasive

1. Montorsi et al. J Urol 1997; Mulhall et al. JSM 2005
Montorsi (1987) reported that treatment with ICI alprostadil (5mcg, 2-3/week) initiated 4 weeks after NSRRP was associated with a return of spontaneous erections in 67% of men as opposed to only 20% of controls [1]

The study suffers from methodological flaws

Pre-dated validated EF questionnaires ... no pre- or post-operative testing or questionnaire, incomplete reporting of NPT and penile Doppler data

Intuitively appealing but is limited by the small study group and yet to be duplicated in a placebo controlled fashion or on a larger scale

The Use of an Erectogenic Pharmacotherapy Regimen Following Radical Prostatectomy Improves Recovery of Spontaneous Erectile Function

John Mulhall, MD, * Spencer Land, MD, † Marilyn Parker, MD, † W. Bedford Waters, MD, † and Robert C. Flanigan, MD †

- 136 sildenafil refractory post-RP ED patients were either offered ICI rehabilitation or no rehabilitation
- At 18/12 post RP, rehabilitation group had higher % of patients capable of unassisted intercourse and of sildenafil responders vs. no rehabilitation group

<table>
<thead>
<tr>
<th></th>
<th>Rehabilitation group</th>
<th>No rehabilitation group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 58)</td>
<td>(n = 74)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with functional erections (nonmedication assisted)†</td>
<td>52%</td>
<td>19%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Patients responding to sildenafil‡</td>
<td>64%</td>
<td>24%</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Patients responding to intracavernosal injections‡</td>
<td>95%</td>
<td>76%§</td>
<td>&lt;0.01*</td>
</tr>
</tbody>
</table>

The Use of an Erectogenic Pharmacotherapy Regimen Following Radical Prostatectomy Improves Recovery of Spontaneous Erectile Function

John Mulhall, MD,* Spencer Land, MD,† Marilyn Parker, MD,† W. Bedford Waters, MD,† and Robert C. Flanigan, MD†

- In addition, the rehab group had higher mean IIEF erectile function domain scores at 18/12 post RP

<table>
<thead>
<tr>
<th></th>
<th>Rehabilitation group (n=58)</th>
<th>No rehabilitation group (n=74)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 months post RP†</td>
<td>8 ± 1.4</td>
<td>9 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td>≤18 months post RP</td>
<td>22 ± 6.6</td>
<td>12 ± 14.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients with normal EFD score‡</td>
<td>22%</td>
<td>6%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Patients with severe ED‡</td>
<td>14%</td>
<td>38%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- Subjects who started ICI within the 1/12 of surgery had a better erectile response than those who started receiving 2–3/12 post-RP

Vacuum Constriction Devices

- Effective as ED treatment
- No convincing animal or human data to support any role in post-RP EF rehabilitation
- VCD causes corporal ischaemia [1,2], acidotic non-arterial corporal blood and a lack of SM relaxation [3]
- ? Role of penile stretch
- Use of VCDs may actually delay effective Rx

Early use of vacuum constriction device following radical prostatectomy facilitates early sexual activity and potentially earlier return of erectile function

R Raina\textsuperscript{1,2}, A Agarwal\textsuperscript{1}, S Ausmundson\textsuperscript{1}, M Lakin\textsuperscript{1}, KC Nandipati\textsuperscript{1}, DK Montague\textsuperscript{1}, D Mansour\textsuperscript{2} and CD Zippe\textsuperscript{1}

- 74 post RP patients used a VCD daily for 9 months vs. 35 men with no treatment
- 60/74 (81\%) successfully used VCD for intercourse
- The results were inconclusive ...

<table>
<thead>
<tr>
<th></th>
<th>VCD (n=60)</th>
<th>Control (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return of erections at 9/12</td>
<td>19 (32%)</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Sufficient erection for penetration</td>
<td>10 (17%)</td>
<td>4 (11%)</td>
</tr>
</tbody>
</table>
Pharmacological Neuromodulation

- The use of drugs to provide neuroprotection and neuroregeneration before and after nerve injury
- Restore CN function and promote erection recovery after RP
- The rat models of cavernous nerve crush injury provide the vehicles for investigation of neuroprotective agents [1-3]
- Multiple potential neuroprotective agents including immunophilin ligands, rapamycin, minocycline, erythropoietin and PDE5i

Neuroimmunophilin Ligands Protect Cavernous Nerves after Crush Injury in the Rat: New Experimental Paradigms

Heather Valentine\textsuperscript{a}, Yi Chen\textsuperscript{a}, Hongzhi Guo\textsuperscript{a}, Jocelyn McCormick\textsuperscript{a}, Yong Wu\textsuperscript{a}, Sena F. Sezen\textsuperscript{b}, Ahmet Hoke\textsuperscript{c,d}, Arthur L. Burnett\textsuperscript{b}, Joseph P. Steiner\textsuperscript{c,*}

- Neuroimmunophilin ligand GPI-1046 (GPI) from Guildford pharmaceuticals
- Intraperitoneal and oral GPI to rats 30 min before CN crush injury maintained ICP and provided nearly complete erectile protection
Neuroimmunophilin Ligands Protect Cavernous Nerves after Crush Injury in the Rat: New Experimental Paradigms

Heather Valentine, Yi Chen, Hongzhi Guo, Jocelyn McCormick, Yong Wu, Sena F. Sezen, Ahmet Hoke, Arthur L. Burnett, Joseph P. Steiner

- GPI prevents degeneration of ~ 83% of unmyelinated axons at 7 days post CN injury

   Eur Urol 51 (2007) 1724–1731
Tacrolimus (FK-506) RCT in RP Patients
Principal Arguments in Favour of Penile Rehabilitation

• Signals from animal and human studies are clear & robust

• ED associated with depression and reduced QOL

• Apathy leads to time-dependent structural changes in CCSM

• Sexual medicine experts are routinely doing rehabilitation post-RP
Principal Arguments Against Penile Rehabilitation

- Unproven strategy - Lack of level I EBM
- Translating animal data to human model
- Cost
PRE-OP ASSESSMENT & EDUCATION

PDE5i AT CATHETER REMOVAL
MAX DOSE PDE5i x4/WEEK FOR 2-4/52 + LOW DOSE PDE5i OTHER NIGHTS

PDE5i FOR 2/52 PRE-OP
MAX DOSE PDE5i x4/WEEK FOR 2-4/52 + LOW DOSE PDE5i OTHER NIGHTS

REVIEW 4/52 POST-OP

PDE5i RESPONDER
OD SIL 100/VAR 20 + SIL25/VAR10 x4/WK
TAD 10-20 x3/WEEK +/- OD TAD 20

PDE5i NON-RESPONDER
ICI TRIMIX 2-3/WEEK + LOW DOSE TAD
RE-CHALLENGE WITH OD PDE5i EVERY 2/12
SWITCH FROM ICI TO PDE5i OR CONTINUE ICI TRIMIX

FOLLOW-UP EVERY 4/12 FOR 30/12
Thank You