Recovery Sexual Function After Prostate Cancer

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Disclosures

• Consultant - Endo, Coloplast, Boston Scientific
• Research support - Tissue Genesis
Are Urologist Implementing Erection Preservation Programs?

• Survey of 301 Urologists from 41 countries: 83.7% offered some type of erection preservation program
  - 95.4% - PDE-5i
  - 75.2% - ICI
  - 30.2% - VED
  - 9.9% - MUSE

• Reasons for not initiating a program
  - 50% - cost
  - 25% - not evidence based

ERECTILE DYSFUNCTION: AUA GUIDELINE

Arthur L. Burnett, MD; Ajay Nehra, MD; Rodney H. Breau, MD; Daniel J. Culkin, MD; Martha M. Faraday, PhD; Lawrence S. Hakim, MD; Joel Heidelbaugh, MD; Mohit Khera, MD; Kevin T. McVary, MD; Martin M. Miner, MD; Christian J. Nelson, PhD; Hossein Sadeghi-Nejad, MD; Allen D. Seftel, MD; Alan W. Shindel, MD
Prior ED Treatment Paradigm

Male patient diagnosed with ED

1\textsuperscript{st} line therapies

Oral ED therapies (PDE5i)

~75 %

2\textsuperscript{nd} line therapies

Urethral suppository

Injectable

Vacuum pump

~5%  <10%  <5%

3\textsuperscript{rd} line therapies

Penile implant

Corrective vascular surgery

~5%  <1%  

Prescribed by both Urologists & PCPs

Primarily prescribed by Urologists

Source: Adapted from American Urologic Association Treatment of ED Guidelines, emedicine.com, L.E.K. Consulting Interviews and analysis.
ERECTILE DYSFUNCTION ALGORITHM

COUNSEL THE MAN AND PARTNER REGARDING:
- The value of psychosocial/relationship support from trained professionals to optimize treatment satisfaction
- The importance of lifestyle change (weight loss, exercise, smoking cessation)
  to improve erectile function and overall health
- The benefits and risks/burdens of all available ED treatments that are not contraindicated

Using a shared decision-making framework, identify appropriate treatment based on values and priorities of man and partner

- PDE5i
- Vacuum devices
- Intracavernosal (IU) alprostadil
- Intracavernosal injections (IC)
- Penile prosthesis surgery

ASSESS OUTCOMES, ADVERSE EVENTS (AEs), AND SATISFACTION OF MAN AND PARTNER

IF INADEQUATE EFFICACY AND/OR UNACCEPTABLE AEs AND/OR INSUFFICIENT SATISFACTION, THEN ADDRESS AS APPROPRIATE:
- Dose adjustments (for PDE5i, IU alprostadil, IC)
- Revisit instructions to maximize efficacy (for all treatments)
- Revisit values and priorities of man and partner with mental health professional to refine values and priorities and/or to address psychosocial or relationship barriers to successful treatment
- Consider alternate treatment.
Are We Treating Men Too Late After Prostatectomy?

- 19 men with history of BNS RP
- All men documented good erections before surgery with confirmatory RigiScan
- No penile rehabilitation
- Corporal biopsy at time of RP and 2 and 12 months after surgery
- At 2 months, significant decrease in smooth muscle and elastic fibers and increase in collagen
- At 12 months, 60% increase in collagen and a 65% decrease in elastic fibers in the corporal smooth muscle

Are We Treating Men Too Late After Prostatectomy?

- Mulhall et al.¹
  - The incidence of post-RP venous leak was time dependent:
    - 14% at 4 months
    - 30% at 8 months
    - 50% at 12 months

- Mulhall et al. ²
  - Predictors of outcomes with penile rehabilitation after RP
  - Highest risks of failure for return of natural erections:
    - Non-nerve sparing procedure
    - Trimix dose >0.50cc
    - Age >60 years
    - Presence of >1 vascular co-morbidity
    - Commencement of penile rehabilitation >6 months post RP

- McCullough et al. ³
  - Men who presented for treatment with ED one year after RRP had no return of natural function (satisfactory and sustained erections)

³ McCullough et al. Urology. 2002 Sep;60
Is Penile Rehabilitation Effective?
Effect of Sildenafil on Intracorporeal Smooth Muscle Following Radical Prostatectomy

• After RRP:
  • 11 patients taking sildenafil 50 mg qod
  • 10 patients taking sildenafil 100 mg qod
    • Rx started after catheter removal
    • Continued for 6 months post op

• Intracorporeal muscle biopsy prior to RRP and at the end of 6 months

### Intracorporeal Muscle Biopsies (% normal smooth muscle*)

<table>
<thead>
<tr>
<th></th>
<th>RRP</th>
<th>6 month post-RRP</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil 50 mg</td>
<td>51.5%</td>
<td>52.7%</td>
<td>0.81</td>
</tr>
<tr>
<td>Sildenafil 100 mg</td>
<td>42.8%</td>
<td>56.9%</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

*Normal ≥ 40%

## Penile Rehab – PDE$_5$

<table>
<thead>
<tr>
<th>Authors</th>
<th>PDE$_5$ – I</th>
<th>Study Design</th>
<th>N</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pace et al 2010</td>
<td>Flexible-dose sildenafil</td>
<td>Randomized, controlled</td>
<td>40</td>
<td>Successful intercourse: 54% vs 21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6 months</td>
<td></td>
<td>Normal erection: 34% vs 18%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Responders to sildenafil: 72% vs 32%</td>
</tr>
<tr>
<td>Mulhall et al 2005</td>
<td>Sildenafil 100mg (3x per week)</td>
<td>Non-R, comparing rehab vs non-rehab, 18 months</td>
<td>132</td>
<td>Natural erections: 52% vs 19%</td>
</tr>
<tr>
<td></td>
<td>Nonresponders ICI</td>
<td></td>
<td></td>
<td>Sildenafil response: 64% vs 24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ICI response: 95% vs 76%</td>
</tr>
<tr>
<td>Bannowsky et al 2008</td>
<td>Daily sildenafil</td>
<td>Non-R, 12 months</td>
<td>41</td>
<td>Spontaneous erection: 47% vs 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Assisted erection: 86% vs 66%</td>
</tr>
<tr>
<td>Padma – Nathan et al 2008</td>
<td>Nightly sildenafil</td>
<td>Randomized, double-blind, Control, 9 months + 2</td>
<td>76</td>
<td>Normal erection: 27% vs 4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>month wash-out</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aydogdu et al 2011</td>
<td>Tadalafil 3d/wk</td>
<td>RCT 12 months</td>
<td>65</td>
<td>Significant size preservation</td>
</tr>
<tr>
<td>Montorsi et al 2008</td>
<td>Nightly vs OD vardenafil</td>
<td>Randomized, double-blind, Control, 9m with 2m</td>
<td>628</td>
<td>No difference between rehab group and control group.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>wash-out</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Lee et al. BJU Int 105: 382, 2010
AUA ED Guidelines: Penile Rehab

- Men who desire preservation of erectile function after treatment for prostate cancer by radical prostatectomy (RP) or radiotherapy (RT) should be informed that early use of PDE5i post-treatment may not improve spontaneous, unassisted erectile function. (Moderate Recommendation; Evidence Level: Grade C)
Androgens and Erectile Function: A Case for Early Androgen Use in Postprostatectomy Hypogonadal Men

Mohit Khera, MD, MBA, MPH
Baylor College of Medicine—Department of Urology, Houston, TX, USA
DOI: 10.1111/j.1743-8109.2008.01159.x
AUA ED Guideline Statements: Testosterone Treatment

• Men with ED and testosterone deficiency (TD) who are considering ED treatment with a PDE5i should be informed that PDE5i may be more effective if combined with testosterone therapy. (Moderate Recommendation; Evidence Level: Grade C)
T and Prostate Cancer

**AUA 2018 Guidelines**

Clinicians should inform patients of the absence of evidence linking testosterone therapy to the development of prostate cancer. *(Strong Recommendation; Evidence Level: Grade B)*

Patients with testosterone deficiency and a history of prostate cancer should be informed that there is inadequate evidence to quantify the risk-benefit ratio of testosterone therapy *(Expert Opinion)*

**Endocrine 2018 Guidelines**

We recommend against testosterone therapy in men with.... prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level >4 ng/mL, a prostate-specific antigen level >3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation)....severe lower urinary tract symptoms,.... *(Low quality evidence)*
The Female Factor: Predicting Compliance with a Post-Prostatectomy Erectile Preservation Program

Daniel J. Moskovic, MA,*† Osama Mohamed, MD,* Kumaran Sathyamoorthy, MD, MPH,* Brian J. Miles, MD,* Richard E. Link, MD, PhD,* Larry I. Lipshultz, MD,* and Mohit Khera, MD, MBA, MPH*

*Baylor College of Medicine—Scott Department of Urology, Houston, TX, USA; †Columbia Business School, NY, USA

DOI: 10.1111/j.1743-6109.2010.02014.x
Erectile Dysfunction: Unmet Medical Need

- Most important considerations when starting ED medications:

- Most important reasons for discontinuing ED medications:

<table>
<thead>
<tr>
<th>Reasons for discontinuation (quantitative data)</th>
<th>%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-effectiveness</td>
<td>38.0</td>
</tr>
<tr>
<td>Erection recovery</td>
<td>22.3</td>
</tr>
<tr>
<td>Concerns about cardiovascular safety of PDE5</td>
<td>15.7</td>
</tr>
<tr>
<td>Cost</td>
<td>13.7</td>
</tr>
<tr>
<td>Secondary effects</td>
<td>12.3</td>
</tr>
<tr>
<td>Lack of sexual opportunity</td>
<td>11.5</td>
</tr>
<tr>
<td>Other treatments</td>
<td>9.3</td>
</tr>
<tr>
<td>Lack of spontaneity</td>
<td>8.7</td>
</tr>
<tr>
<td>Fear of drug dependence</td>
<td>6.0</td>
</tr>
<tr>
<td>Decreased sexual interest</td>
<td>5.4</td>
</tr>
<tr>
<td>Constrain/embarrassment in obtaining the drug</td>
<td>2.7</td>
</tr>
</tbody>
</table>

Hanson-Divers et al J Urol 1998;159:1541-1547;
Shockwave Therapy to Treat ED
Shockwave Therapy to Treat Other Medical Conditions

- Plantar fasciitis
- Achilles tendonitis
- Myocardial revascularization
Different Forms of Shockwave Generators

- Radial pressure wave (RSWT)
- Electrohydraulic shockwave
- Electromagnetic shockwave
- Piezoelectric shockwave
- Pneumatic shockwave

Courtesy of F. Giuliano
Cavernosal Tissue Response to Shockwaves

Activate nerve repair

Activate resident stem cells

Restore normal endothelial signaling

Recruit immune cells, initiate wound healing

Recruit stem cells
• **Single-arm trials** almost unanimously show beneficial effects in patients with vasculogenic ED, even in PDE5i non-responders

• **RCTs** have produced conflicting results, and have evaluated erectile function only a short time after treatment; several RCTs are highly biased

• **Meta-analyses and systematic reviews** conclude that shockwave therapy has an effect, but these analyses are limited by the fact that biased RCTs have been included in these analyses
  
  • No high-quality level 1a evidence is available and level 1b evidence is conflicting regarding the use of Li-ESWT for ED treatment

• **CONCLUSION:** Li-ESWT should be limited to clinical trials until large multi-centric RCTs have provided the necessary data to recommend the routine use of this promising novel technology as a first-line treatment

For men with ED, low-intensity extracorporeal shock wave therapy (ESWT) should be considered investigational. (Conditional Recommendation; Evidence Level: Grade C)
Emerging Tools for Erectile Dysfunction: A Role for Regenerative Medicine

Effects of Mesenchymal Stem Cells on Cavernous Smooth Muscle

Smooth

Fibrosis

Nerve

Summary of Published Clinical Trials on Stem Cells for ED

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Number of men</th>
<th>Cause of ED</th>
<th>Treatment</th>
<th>Assessment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bahk (2010) [53]</td>
<td>7</td>
<td>Diabetes</td>
<td>Umbilical blood SC</td>
<td>IIIEF-5, SEP, GAQ</td>
<td>Improved rigidity in 2/7, able to penetrate with PDE5i</td>
</tr>
<tr>
<td>Levy (2016) [67]</td>
<td>8</td>
<td>Organic</td>
<td>Placental-derived SC</td>
<td>PSV, IIIEF</td>
<td>3/8 improved erection; IIIEF change not significant</td>
</tr>
<tr>
<td>Haahr (2016) [52]</td>
<td>17</td>
<td>5~18 months after radical prostatectomy</td>
<td>Adipose-derived SC</td>
<td>IIIEF-5</td>
<td>8/11 continent men and 0/6 incontinent men recovered erection</td>
</tr>
<tr>
<td>Yiou (2016) [51]</td>
<td>12</td>
<td>22 months after radical prostatectomy</td>
<td>Bone marrow mononuclear cells</td>
<td>IIIEF-15, EHS, color Doppler ultrasound</td>
<td>1/12 hard erection; 9/12 needed ICI, PDE5i, or VCD. Improved EHS and IIIEF</td>
</tr>
</tbody>
</table>


Reed-Maldonado et al. World J Mens Health 2016: 34(3):155-164
Safety of Intercavernous Bone Marrow-Mononuclear Cells for Post-radical Prostatectomy Erectile Dysfunction: An Open Dose-Escalation Pilot Study

- 12 men with ED not responding to medication
- All men had radical prostatectomy 6 to 36 months earlier
- Mean age 63.6 years
- 4 different dosages of mononuclear BM stem cells injected once into corpora
  - 20,000,000
  - 200,000,000
  - 1,000,000,000
  - 2,000,000,000

Results:
- No serious adverse events
- 75% of men reported successful intercourse on medication
- No significant differences in erectile function scores among 4 doses
  - Greatest improvement in erectile hardness scores seen with 2 highest doses compared to 2 lowest doses
Safety and Potential Effect of a Single Intracavernous Injection of Autologous Adipose-Derived Regenerative Cells in Patients with Erectile Dysfunction Following Radical Prostatectomy: An Open-Label Phase I Clinical Trial

- 17 men with ED not responding to medication
- All men had radical prostatectomy 5-18 months earlier
- Median age 69 years
- One corporal injection of 8.4–37.2 million autologous ADSC

**Results:**
- No serious adverse events
- 8 of 17 men recovered their erectile function
  - Continent men 8/11 recovered erectile function
  - Incontinent men 0/6 recovered erectile function

Haahr et al. EBioMedicine: 2016 Jan 19; 5:204-10
Word of caution...

- Only 4 small clinical trials published in the literature
  - No control group
  - No randomization
- Further larger randomized controlled trials are desperately needed in this field
F.D.A. Cracks Down on ‘Unscrupulous’ Stem Cell Clinics
AUA ED Guidelines: Stem cells

For men with ED, intracavernosal stem cell therapy should be considered investigational. (Conditional Recommendation; Evidence Level: Grade C)
Baylor College of Medicine
Stem Cell and ED Studies

Human trials:
- IRB and FDA approved clinic trial (NCT01601353)
- Randomized controlled trial
- Diabetic and radical prostatectomy patients
- Autologous adipose derived stem cells
- 30 patients completed study

Animal experiments:
- IRB approved experiments
- Diabetic rat model
- Autologous adipose derived stem cells
- Assessing optimal dosing and frequency of intracavernosal stem cell injections
# ED IIa vs. IIb Study Key Parameters Comparison

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>IIa</th>
<th>IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>Treatment or Control</td>
<td>Treatment then Sham or Sham then Treatment</td>
</tr>
<tr>
<td>Number of Subjects</td>
<td>30 (20 treated)</td>
<td>60 (all treated)</td>
</tr>
<tr>
<td>Blinding</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Starting IIEF-EF</td>
<td>&lt; 26</td>
<td>11-22</td>
</tr>
<tr>
<td>PDE-5 Use During Study</td>
<td>Not Allowed</td>
<td>Allowed But Not Required</td>
</tr>
<tr>
<td>Primary Endpoint Timeframe</td>
<td>6 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Imaging</td>
<td>None</td>
<td>Doppler</td>
</tr>
</tbody>
</table>
Platelet Rich Plasma
PRP Statistics

- No studies listed on www.clinicaltrials.gov for PRP and ED

- Google “Platelet rich plasma, erectile dysfunction”: 147,000 results (10/2017)

- Website marketing (2015) “bigger erections, improved sex life, improvement in climax/orgasm, increased sensation, increased libido” and “improved sensation even years after prostatectomy”

- Cost: $1500 to $3000 cash per injection

- 2018 first PRP/ED study published (case series)

Jenkins L et al. 2015 JSM 12(12) 2223-2225
Franco M, Garcia-Cruz E ESSM 2018
• 4 with ED only and 1 with ED and Peyronies disease
• Between 4 and 9 mL of PRP was injected in corpora cavernosa per treatment session.
• A mean of 2.1 injection procedures per patient were performed
• IIEF-5 improvement of 4.14
• AEs (in all patients): mild pain (23.5%) and bruising (5.9%)
7. HOW CAN PLATELET RICH PLASMA (PRP) TREAT ERECTILE DYSFUNCTION?

The Priapus Shot, a revolutionary new procedure from the creators of the popular Vampire Facelift, can treat erectile dysfunction using platelet rich plasma (PRP). The Priapus Shot procedure is non-invasive and doesn’t carry the heart-health risks that many traditional erectile dysfunction treatments do.

The Priapus Shot uses natural, regenerative cells that are drawn from your bloodstream. These cells are refined to make the platelet rich plasma (PRP), using a highly-advanced centrifuge.

By administering platelet rich plasma directly to the penis, the Priapus Shot (also called the M-Shot) delivers erections that are:

- Firmer
- Larger
- More frequent
- Longer-lasting

Through PRP, the Priapus Shot promotes the growth of new tissue. The results of the Priapus Shot can help you have better erections for up to 18 months or longer. If you’re interested in finally beating erectile dysfunction with the Priapus Shot, call...

Click here for the erectile dysfunction intensity scale.

The concept of penile rehabilitation was first studied by Mononi et al. in 1997.

This recent study showed that using vasodilators combined with a penis pump improved erectile function post-prostatectomy.

We’re seeing an average improvement of 5-8 on an ED scale using a pump combined with PRP (the Priapus Shot procedure).
AUA ED Guidelines: Platelet Rich Plasma

For men with ED, platelet-rich plasma (PRP) therapy should be considered experimental. (Expert Opinion)
Conclusion

• Current ED therapies do not provide a “cure” for ED

• Early use of PDE5i post-treatment may not improve spontaneous, unassisted erectile function

• The mechanisms for how PRP, stem cells and LIST improve erectile dysfunction appear to be promising and some initial studies have demonstrated benefit

• At this time, the use of LIST, stem cells or PRP should be considered experimental until appropriate RCTs have demonstrated proven efficacy and safety
Thank You

Texas Medical Center, Houston