Penile Rehabilitation after Radical Prostatectomy

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Post-Radical Prostatectomy Sexual Dysfunctions

- Erectile dysfunction (ED)
- Anejaculation
- Anorgasmia
- Dysorgasmia (painful ejaculation)
- Orgasm associated urine leak (climacturia)
- Penile length alterations
- Penile curvature
Sexual Dysfunction After Radical Prostatectomy

- Despite nerve-sparing surgery RP leaves 25 to 75% of patients with ED (Hollenbeck et al. 2003; Cooperberg et al. 2003; Schover et al. 2002; Meyer et al. 2003; Hu et al. 2004; Penson et al. 2005)
- Meta-analysis: 54 long-term studies found 75% with ED at least 2 years post-RP (Robinson et al. 2002)
- Stanford Study (n=1291): 40% to 55% of bilateral NS patients experienced ED at 18 mos (Stanford et al. 2000)
- Penson Study (n=1288): found 72% with ED at least 5 years post-RP (Penson et al. 2005)

  - Long-term ED post RP: 40% to 75% (Matthew et al. 2005)

Risk Factors of Post-Prostatectomy ED: Patient Factors

- Age more than 60 years
- Vascular diseases
- Diabetes
- Dyslipidemia
- Smoking
- High stage of disease
- Non-motivated partner
- PDE5-I user
- Obesity

Assessment of a patient's preoperative erectile function is essential.

Using a validated questionnaire, e.g. International Index of Erectile Function (IIEF) may help diagnose and determine the severity of erectile dysfunction
Is it a ‘real’ Problem:  
Distress specific to Sexual Dysfunction Post-RP

- Distress re SD: 60% of patients reported moderate to severe distress (Stanford et al. 2000; Cooperberg et al. 2003; Schover et al. 2002)

- In a quality of life study on 1-year post-surgery patients:
  - only 12% reported fear of cancer recurrence
  - 40% reported sexual dysfunction concerns (Heathcote et al. 1998)

- Distress is especially elevated in younger men (Cooperberg et al. 2003; Stanford et al. 2000)

- Partners experience greater distress (Neese, L. E., 2003)

Potency Recovery after Surgery  
Memorial Sloan Kettering

- N=200 potent men
- Bilateral NSRRP (July 1998 - April 2002)

- Completed follow-up IIEF up to 51 months
- 49% used PDE5 inhibitors post-op
- Actuarial rates of recovery of potency to 4 years

Rabbani et al., AUA 2004
Potency Recovery after Surgery

Maximal recovery after bilateral NSRRP may take up to 4 years

Recovery of Erections According to Preoperative Sexual Functioning

Agents/Devices…solution??

Assistive aids vary in invasiveness and effectiveness:
1) Oral Medications (PDE-5 inhibitors)
   - effectiveness in post-RP patients 30-60% (Brock 2003, Montorsi 2004,
     Cavallini 2005, Montorsi 2008)
2) Intracavernous Injections
   - effectiveness in post-RP patients 85% (Hanash 1997)
3) Micro-suppositories
   - effectiveness in post-RP patients 57% (Costabile et al. 1998)
4) Vacuum device
   - effectiveness in post-RP patients 80% (Raina et al. 2002)
5) Penile implant
   - satisfaction rates of 85% (Carson et al. 2000)

Low rates of ongoing use

• The high success rates assistive aids are offset by low rates of
  ongoing use

• Only 20-40% of men remain sexually active at 1-5 yrs. post-RP
  despite access or attempted use of pro-erectile aids/devices (in
  many cases 2 or more aids) (Hanash 1997; Althof 2002; Hu et al. 2004; Penson 2005)
**Post-RP ED Mechanisms**

- **Neurogenic**
  - Degree/type of trauma required for neuropraxia?
  - Anatomic vs functional integrity
  - Neural trauma leads to structural changes in erectile tissue
  - Denervation apoptosis

- **Arteriogenic**
  - Arterial injury (accessory pudendal arteries)

- **Venogenic**
  - Cavernosal hypoxia-induced fibrosis with venous leak

- **Psychogenic**
  - Impact of cancer diagnosis on erectile function
  - Impact of anxiety centered on re-initiation of intimacy


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**Cavernosal Oxygenation**

<table>
<thead>
<tr>
<th>Flaccid</th>
<th>Erect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaccid</td>
<td>Penile erection</td>
</tr>
<tr>
<td>$pO_2 = 35$ mm Hg</td>
<td>$pO_2 &gt; 70$ mm Hg</td>
</tr>
<tr>
<td>Increased TGF secretion</td>
<td>Increased PGE secretion</td>
</tr>
<tr>
<td>Collagen production</td>
<td>Decreased collagen production</td>
</tr>
</tbody>
</table>

PGE=prostaglandin E.  
TGF=transforming growth factor.
Postprostatectomy ED: Proposed Mechanism

Arterial injury → Reduced/absent erection → Neural injury
- Prolonged venous $pO_2$
- TGF-β overexpression
- Excess collagen production
- Structural alterations
  → Erectile tissue apoptosis

Anxiety/stress → Incomplete corporal musc expansion
- Subtunical venule decompression
- Venous leak

What is penile rehabilitation?

- Penile rehabilitation is performed with the aim of achieving better and/or earlier spontaneous erectile recovery compared with no rehabilitation by:
  - Preservation of penile smooth muscle
  - Preservation of endothelial function
  - Optimization of cavernous nerve recovery
Penile Rehabilitation

Central to the argument supporting Rehab:
1. Apoptosis (nerve injury)
2. Loss of NPT (oxygen)
3. Compensation by early therapy
   • Endothelial benefits
   • Enhanced nerve regeneration
   • Preservation of cavernous smooth muscle

Systemic Hypoxia
Reduced Erection Hardness (ICP)

- Systemic hypoxia reduces ICP
- Illustrates importance of sufficient penile oxygenation for effective nitrergic signalling (i.e. induction and maintenance of penile erection)

**Sildenafil Overcame Systemic Hypoxia-Induced ED**

**Pre-clinical model**

![Graph showing the effect of Sildenafil on intracavernosal pressure (ICP) and flow in different oxygen concentrations.](image)


**Alprostadil Injection study**

Montorsi et al., J Urol 1997; 158: 1408-1410

- 30 patients randomized
- Group 1 (n=15): alprostadil injections 3 times/week for 12 weeks
- Group 2 (n=15): observation without erectaids

- Patient-reported recovery of spontaneous erections sufficient for satisfactory sexual intercourse
Alprostadil Injections
Results

Montorsi et al., J Urol 1997; 158: 1408-1410

Hypothesis:
Nightly Post-Operative Sildenafil Dramatically Improves the Return of Spontaneous Erections Following a Bilateral NS-RRP

**Methodology**

- Double-blind, placebo controlled, multicentre, randomized clinical trial
- 76 men (≤65 yrs) with normal preoperative EF
- Combined score of ≥8 for IIEF questions 3 & 4
- Normal nocturnal penile tumescence (NPT)
- Scheduled to undergo a bilateral NSRRP
- 50 mg, n=23; 100 mg, n=28; Placebo, n=25

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**Prevention Study Design**

- Preoperative assessment (1-4 weeks)
- Recovery period (4 weeks)
- Postoperative drug treatment (36 weeks)
- Drug-free postoperative assessment (8 weeks)

- Surgery
- Start drug
- End drug

Padma-Nathan H et al. AUA 2003, Chicago
**Effects of nightly sildenafil treatment on recovery of spontaneous erections: results**

Nightly sildenafil (50–100 mg) vs placebo after 36 weeks of treatment

![Bar chart showing responders to nightly sildenafil and placebo](chart1.png)

1. **Placebo**: n=25
2. **Sildenafil**: n=51

\[ p=0.0156 \]

*Responders: patients with combined IIEF Q3/4 score of ≥8 and positive response to question: “Over the past 4 weeks, have your erections been good enough for satisfactory sexual activity?” at 8 weeks after discontinuation of drug

Padma-Nathan et al. AUA 2003, Chicago.

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**Potency rate following treatment with nightly sildenafil 25 mg (1 year) followed by sildenafil on-demand**

43 patients; 95% had nocturnal erections 2 weeks after surgery

![Bar chart showing patients able to achieve and maintain erection](chart2.png)

1. **Control group**: n=20
2. **Sildenafil**: n=23

\[ Yes (%) \]

*Control group took no medication before the on-demand period

Limitations of existing studies

• Padma-Nathan et al. 2003:
  – Small sample size (N=76)
  – Single centre
  – Did not compare nightly dosing with on-demand use of a
    PDE-5 inhibitor

• Bannowsky et al. 2008
  – Small sample size (N=43)
  – Single centre of surgical excellence – does not reflect general worldwide
    urological practice
  – Not placebo-controlled
  – 95% of patients had nocturnal erections following catheter removal – not
    typical of post-surgical situation in general urological practice

Recovery of erections – intervention with vardenafil
early nightly therapy (REINVENT): study design

**REINVENT: study endpoints**

**Primary endpoint:**
- % of subjects with IIEF-EF domain score ≥22 after 9 months of double-blind treatment plus 1–2 months of single-blind treatment

**Secondary endpoints:**
- Measures of erectile function
  - Mean per-patient success rates from diary questions (SEP2 and SEP3)
  - IIEF-EF domain score of ≥17, ≥22, ≥26
  - IIEF domain total scores
  - RigiScan at select sites
- Quality of life measures
  - Center for Epidemiologic Studies Depression Scale (CES-D)
  - Duke Health Questionnaire
- Other measures
  - Vascular biomarkers
  - Flaccid and stretched penile length


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**REINVENT: Centers (88) and Countries (15)**

<table>
<thead>
<tr>
<th>Country</th>
<th>Centers</th>
<th>Patients*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>Belgium</td>
<td>6</td>
<td>62</td>
</tr>
<tr>
<td>Canada</td>
<td>11</td>
<td>90</td>
</tr>
<tr>
<td>Switzerland</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Germany</td>
<td>12</td>
<td>184</td>
</tr>
<tr>
<td>Spain</td>
<td>7</td>
<td>64</td>
</tr>
<tr>
<td>Finland</td>
<td>3</td>
<td>68</td>
</tr>
<tr>
<td>France</td>
<td>5</td>
<td>88</td>
</tr>
<tr>
<td>UK</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>Italy</td>
<td>8</td>
<td>140</td>
</tr>
<tr>
<td>Netherlands</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Norway</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>Sweden</td>
<td>6</td>
<td>65</td>
</tr>
<tr>
<td>USA</td>
<td>11</td>
<td>101</td>
</tr>
<tr>
<td>South Africa</td>
<td>5</td>
<td>45</td>
</tr>
</tbody>
</table>

*number of patients enrolled

**REINVENT: patient disposition**

Patients enrolled
\( (n=997) \)

Patients randomised
\( (n=628) \)

Patients completed study
\( (n=423) \)


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**REINVENT: patient baseline characteristics**

*(mITT population)*

<table>
<thead>
<tr>
<th>Mean values</th>
<th>Total N=445</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>57.1</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.9</td>
</tr>
<tr>
<td>Baseline IIEF-EF score*</td>
<td>28.5</td>
</tr>
<tr>
<td>Marital status (%):</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>91</td>
</tr>
<tr>
<td>Divorced</td>
<td>5</td>
</tr>
<tr>
<td>Widowed</td>
<td>2</td>
</tr>
<tr>
<td>Never married</td>
<td>2</td>
</tr>
</tbody>
</table>

*Pre-surgery baseline measurement

*mITT population* (patients with at least one IIEF-EF measurement during the single-blind placebo washout period)
**REINVENT: results from double-blind treatment period**


**REINVENT: IIEF-EF domain score ≥22 (mild ED) over 9 months of treatment**

REINVENT: IIEF-EF domain score ≥22 (mild ED) over 9 months of treatment

*\( p=0.0144 \) for comparison of vardenafil nightly vs placebo
(For all secondary variables, \( p<0.05 \) considered to be nominally significant)

**mITT population**

**REINVENT: IIEF-EF domain score ≥26 (normal EF) over 9 months of treatment***

![Bar chart showing mean per-patient success rates](chart)

- Placebo: 16.8%
- Vardenafil nightly: 20.1%
- Vardenafil on-demand: 36.2%

Number of patients:
- Placebo: n=152
- Vardenafil nightly: n=143
- Vardenafil on-demand: n=149

*p=0.0003 for the comparison of on-demand vs placebo
*p=0.479 for the comparison of nightly vs placebo

*Observed at last observation carried forward (LOCF)

mITT population

Montorsi et al. Eur Urol. 54:924; 2008

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**REINVENT: SEP3 success rates after 9 months of treatment at LOCF***

![Bar chart showing mean per-patient success rates](chart)

- Placebo: 31.1%
- Vardenafil nightly: 40.1%
- Vardenafil on-demand: 52.9%

Number of patients:
- Placebo: n=147
- Vardenafil nightly: n=135
- Vardenafil on-demand: n=144

*p=0.0001 for the comparison of on-demand vs placebo
*p=0.0753 for the comparison of nightly vs placebo

*Observed at last observation carried forward (LOCF)

mITT population

Montorsi et al. Eur Urol. 54:924; 2008
**REINVENT: summary of results from double-blind treatment period**

- At all double-blind visits, a significantly greater proportion of patients in the vardenafil on-demand group had IIEF-EF scores ≥22 compared with the placebo group (p≤0.0001)
  - At double-blind LOCF, a significantly greater proportion of patients in the vardenafil on-demand group had IIEF-EF scores ≥22 compared with the placebo group (p=0.0001)
  - The proportion of patients in the vardenafil on-demand group with IIEF-EF scores ≥22 was significantly greater than the vardenafil nightly group at several visits and at double-blind LOCF (p=0.0065)

- Over the entire double-blind treatment period:
  - Significantly greater mean per-patient SEP3 success rates were observed with vardenafil on-demand compared with placebo (p<0.0001)
  - Significantly greater mean per-patient SEP3 success rates were observed with vardenafil nightly compared with placebo (p=0.0344)


**REINVENT: results from single-blind placebo washout period**

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

No active treatment; patients previously on:

- Placebo: 28.9%
- Vardenafil nightly: 24.1%
- Vardenafil on-demand: 29.1%

All between group comparisons non-significant

mITT population


*Observed at LOCF

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**REINVENT: SEP3 success rates after 2 months of washout**

No active treatment; patients previously on:

- Placebo: 34.5%
- Vardenafil nightly: 32%
- Vardenafil on-demand: 41.5%

All between group comparisons non-significant

mITT population


*Observed at overall single-blind time point
REINVENT: summary of results from single-blind washout period

- The primary efficacy variable was not met:
  - No statistically significant differences between treatment groups in the percentage of patients with IIEF-EF scores ≥22 at end of 2-month washout period (LOCF)
- No significant differences between treatment groups in the proportions of patients with IIEF-EF scores ≥17 or ≥26
- No significant differences between treatment groups in SEP3 mean per-patient success rates

Montorsi et al. Eur Urol. 54:924; 2008

REINVENT: results from open-label period

Montorsi et al. Eur Urol. 54:924; 2008
**REINVENT: IIEF-EF domain score ≥22 after 2 months of open-label on-demand vardenafil treatment***

Patients previously on:

- Placebo
- Vardenafil nightly
- Vardenafil on-demand

<table>
<thead>
<tr>
<th>Patients with IIEF-EF score ≥22 (%)</th>
<th>n=146</th>
<th>n=138</th>
<th>n=142</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>47.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vardenafil nightly</td>
<td></td>
<td>52.6</td>
<td></td>
</tr>
<tr>
<td>Vardenafil on-demand</td>
<td></td>
<td></td>
<td>54.2</td>
</tr>
</tbody>
</table>

*Observed at LOCF

Montorsi et al. Eur Urol. 54:924; 2008

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**REINVENT: SEP3 success rates after 2 months of open-label on-demand vardenafil treatment***

Patients previously on:

- Placebo
- Vardenafil nightly
- Vardenafil on-demand

<table>
<thead>
<tr>
<th>Mean per-patient success rate (%)</th>
<th>n=141</th>
<th>n=127</th>
<th>n=135</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>57.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vardenafil nightly</td>
<td></td>
<td>59.8</td>
<td></td>
</tr>
<tr>
<td>Vardenafil on-demand</td>
<td></td>
<td></td>
<td>62.6</td>
</tr>
</tbody>
</table>

*Observed at last observation carried forward (LOCF)

Montorsi et al. Eur Urol. 54:924; 2008
**REINVENT: summary of results from open-label period**

- No significant differences between the proportions of with IIEF-EF scores ≥22 at LOCF, irrespective of original treatment group
- No significant differences between treatment groups in mean SEP3 per-patient success rates
  - Mean SEP3 per-patient success rates of approximately 60% achieved following 2 months of on-demand vardenafil treatment, irrespective of original treatment group


**REINVENT: adverse events**

- A total of 39 patients discontinued the study due to adverse events (AEs)
- No difference between treatment groups in the percentage of patients that discontinued due to AEs (vardenafil nightly 8%; vardenafil on-demand 6%; placebo 5%)
- Most common AEs were headache, flushing and nasopharyngitis

**REINVENT: Problems**

- Conducted over 3 years at 88 centres; only 423 completed (dropout>30%) so mean # pts per centre <5 (homogeneity of NS technique)
- No documentation of compliance rates in nightly or on-demand groups (Potential confounder: total # of vardenafil pills used in each group?)
- True blinding difficult to achieve in these types of studies (how motivated can these pts be if they stay on 9 months of placebo?)
- Duration of study too short as so many men recover at 18-24 months


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**REINVENT: conclusions**

- In this study, the primary efficacy variable was not met:
  - After 9 months of treatment plus 2 months of washout, nightly dosing with vardenafil did not show any effect beyond that of on-demand use on recovery of erectile function.
- Vardenafil on-demand showed good efficacy in this notoriously difficult-to-treat patient population with ED.
- Vardenafil on-demand was observed to work early after NSRP.
- Methodologic problems do not justify the authors conclusions that the data supports a shift to on-demand PDE5i.
- Need to perform more trials of on-demand vs nightly dosing
**An Approach to Rehab:**
*Pre-Radical Prostatectomy*

- Manage EXPECTATION
- Awareness of potential changes in sexual response
- Awareness of available ED treatments (trial PDE5i)
- Awareness of rationale for early ED treatment approach

**An Approach to Rehab:**
*Immediate post op*

- Early therapy is encouraged
- Based on recent reports we initiate ASAP with low dose PDE5i (sildenafil 25, vardenafil 5-10, tadalafil 5) nightly
- As soon as patient is dry and libido returns, may switch to on-demand dosing
- If rigidity with PDE5i is suboptimal
  - Full dose PDE5i
  - ICI
  - Pump
An Approach to Rehab:  
3 to 6 months post-RP

- Sexual Health Psychotherapy
  - Normalize distress
  - Assessment of partner’s sexual functioning
  - Intimacy Counselling and Couple Communication
  - Resume Sexual Activity (intercourse or non-intercourse)

An Approach to Rehab:  
Beyond 12 months post-RP

- Determine EFFECTIVE ED TREATMENT
- Focus on partner concerns
- Maintenance of INTIMACY and SEXUAL ACTIVITY
- ADAPTATION to changes in sexual response
- ACCEPTANCE of sexual activity (intercourse or non-intercourse)
Improving QOL outcomes after RP

Saguaro cacti (Saguaro erectus)