Sex Rehab after Radical Prostatectomy: Is it Really Justified?

*Con Position*

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Is This Really a Fair Debate?
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What Exactly Are We Debating?

- **NOT DEBATING:**
  - PDE5’s improve erectile function in rats post nerve crush
  - Penile tissue becomes more fibrotic post prostatectomy
  - Use of PDE5’s improves erectile function while on therapy
  - Penile traction / VED improves penile length

- **YES DEBATING:**
  - Treatment of HUMAN males post prostatectomy with PDE5s and/or ICI
    - Improves unassisted erectile function
    - Improves responsiveness to erectogenic aids
    - Restores erectile function sooner than otherwise
    - Prevents loss of erectile function
    - Reduces other sequela (PD)
Quick Primer on Levels of Evidence

Level I is BETTER than Level V
Levels of Evidence – Oxford Criteria

• 1a – Systematic review of homogenous RCTs
• 1b – Individual RCT with narrow CI
• 2b – Individual cohort study (or low quality RCT)
• 3b – Case-control study
• 4 – Case-series
• 5 – Expert opinion, bench research, animal studies
Animal Studies - PDE5s in Nerve Crush Model

- Affects smooth muscle genes
- ↓ oxidative stress
- ↑ survival kinases, cGMP, NO
- ↓ pro-fibrotic TGF-β1
- Neuroprotective

- Improves penile hypoxia
- ↑ smooth muscle content
- ↓ endothelial cell apoptosis

- Prevents venous leak
- ↑ response to penile injection
- ↑ overall erectile function
There is NO question that there is strong Level V evidence arguing for penile rehabilitation
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CEBM; Oxford Levels of Evidence – March 2009.
Trials Supporting Rehab
Pro Rehab RCT, PC Trials

Pace, et al.\textsuperscript{1}

\begin{itemize}
  \item 2 wks
  \item 8 wks treatment
  \item 14 wks washout
\end{itemize}

Results

- N=40, Post-RP
  - Sil 50/100 mg qhs
  - Placebo

\begin{itemize}
  \item IIEF-25.2\textsuperscript{*}
  \item IIEF 17.4
\end{itemize}

\textit{*P<0.05; Medication unassisted intercourse 54% vs 21%}

Pro Rehab RCT, PC Trials

Padma-Nathan, et al.¹

N=76, Post-RP

4 wks

36 wks treatment

8 wks washout

Results

Sil 50 mg qhs

Sil 100 mg qhs

Placebo

26%*

IIEF-12.4

29%*

IIEF-13.7

4%*

IIEF-8.8

*Response – ≥ 8 on Q3-4 IIEF; p=0.02

Pro Rehab RCT, PC Trials

Padma-Nathan, et al.¹

- Meta-analysis, expected placebo response 34% (CI 30-38%)²
- Trial halted prematurely due to lack of response
- Authors hypothesized that low placebo due to strict criteria for response
  - Meta-analysis used similar criteria

*Response – ≥ 8 on Q3-4 IIEF; p=0.02

Pro Rehab RCT, PC Trials

Montorsi, et al.\textsuperscript{1}

N=27, Post-RP

4 wks

12 wks treatment

No washout!

Results

Alprostadil 3x/wk

67\% spontaneous erections\textsuperscript{*}

Observation

20\% spontaneous erections\textsuperscript{*}

\textsuperscript{*}P<0.01

Trials Failing to Support Rehab
Anti Rehab RCT, PC Trials

Montorsi, et al.¹

N=423, Post-RP

Var 10 + PC prn

PC qhs + Var 5-20 prn

Placebo

Results

4 wks

36 wks treatment

8 wks washout

8 wks open-label

Results

Results

*Primary outcome IIEF ≥ 22 after washout


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Take Home Points:
1. Biggest RCT
2. **NO** difference after washout
3. **NO** benefit on subsequent prn response
Dr. Mulhall’s Response to the Study

- Argued weaknesses of methodology
  - Large # of surgeons, poor SEP3 response, no info on vardenafil frequency, likely high drop out rates, difficulty with blinding

**Does on-demand vardenafil improve erectile function recovery after radical prostatectomy?**

John P Mulhall

**SUMMARY**
The randomized, placebo-controlled trial reported by Montorsi and colleagues attempted to determine if nightly vardenafil was more effective than on-demand drug in restoring erectile function after radical prostatectomy. No significant difference in outcomes was found between the study groups at 11 or 13 months after surgery. The study, however, had enough methodological flaws to prevent any definitive conclusions from being drawn. The authors’ conclusion that the data support a shift towards on-demand phosphodiesterase 5 inhibitor use after radical prostatectomy is not supported by the data.

**KEYWORDS** dosing, erectile function, nightly, on demand, prostatectomy
How Does Montorsi Respond?

If you can’t beat them, join them
Montorsi, et al.¹

Screening period
36 wks treatment
6 wks washout
12 wks open-label

N=315, Post-RP

Tad 5 mg qday
Tad 20 mg prn
Placebo

Results

Tad 5 mg qday

Results

Results

*Primary outcome IIEF≥22 after washout

Take Home Points:

1. “The primary objective of the study was not met” - JPM
2. **NO** difference after washout
3. **NO** benefit on subsequent prn response
Maybe it’s an issue of end-point criteria?
Washout
How Can We Argue Against the Evidence?

1. Discredit the methods used
   - Remember, these trials were developed by **leaders in the field** who felt that the protocol was the **optimal** one to achieve positive results
   - Inclusion criteria are **STRICT**
     - This is an **OPTIMAL** group where the best of results would be expected
   - Review of Mayo prostate ca registry:
     - **Only 31%** of patients would meet criteria outlined in the study
     - However, many of our surgeons offer to it ALL patients
     - In other words, the real-life outcomes are likely significantly worse
How Can We Argue Against the Evidence?

2. Argue that the study power is insufficient
   • 124 / group or **372** needed for 90% power\(^1\)
   • 137 / group or **412** for 84% power to detect 20% difference\(^2\)

3. Discredit the messenger – inexperience, youth
   • Remember, Dr. Mulhall trained me!

4. Use anecdotes
   • “Who here does some form of rehab…”

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Summary Pro vs Con RCT/PC Trials

Pro:
- Montorsi (1997), n=27
  - Assessed while still on therapy
- Padma-Nathan (2008), N=36
  - Stopped own trial d/t lack of efficacy
  - Placebo several standard deviations below normal
- Pace (2010), N=40
  - Miraculous IIEF results (baseline) – not repeated in any other study

Con:
- Montorsi (2008), N=423
- Montorsi (2014), N=315
Conclusions

Current data fail to support the use of PDE5s in penile rehab to:

- Improve the extent AND rate of erectile function recovery
- Prophylactically preserve erectile function

Further data are required to:

- Prove the benefit of alternative agents / protocols for rehab
- Support improvements in penile length with pharmacologic rehab
Thank You
Rebuttal
Let’s Return to Our Original Arguments
What Exactly Are We Debating?

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What About Penile Length?

- Yes! Daily tadalafil does improve penile length
- ...by 4 mm
  - 2.8 cubic centimeters (3 cm diameter assumed)
  - 1.76 oz equivalent
  - $1,218/oz gold
  - $2,140 equivalent cost of the increase in size in gold
- Tadalafil daily x 9 months
  - $1,800-2,400
- Other studies fail to demonstrate improved length\(^2\)

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    • Prevents loss of erectile function
    
    • Reduces other sequela (? PD)
      
      • Unknown, Dr. Mulhall would probably have the data for this.
      
      • I hope he can prove this point, because all of the other arguments are crumbling!!!
How About Risks Versus Benefits?

• Positives
  • Better erectile function while on PDE5s
  • Relatively few long-term adverse effects

• Negatives
  • Side Effects
  • Cost – Medications, physician visits
  • Time – Physician visits, injections
  • Blame
    • “My provider didn’t mention rehab, now I have permanent ED”
    • “I didn’t have the money for rehab, and I feel depressed and guilty because of my earlier choices”
Final Statements

• People want to feel like they’re doing something
  • Vitamin E for PD
  • “There’s nothing better, and it probably doesn’t hurt”
  • Placebo was defined in 18th century medicine as, “Any medicine adapted more to please than to benefit the patient.”
  • Derived from Latin, “I shall please”
Final Statements

• Honestly ask yourself, would you buy this product?
  • Costs several thousand dollars
  • Must stick a needle in your penis 3x/weekly
  • Multiple physician visits
  • Majority of data proves that it doesn’t work
Are We Snake Oil Practitioners or Evidenced-based?

• As Andrology specialists and ISSM members, others look to us (everyone in the room) for recommendations as to best practices on penile rehabilitation

• We must base treatment decisions on the available evidence or risk losing credibility

• Context:
  • Far greater evidence for oral colchicine, Potaba, acetyl-l-carnitine, pentoxifylline, Coenzyme Q10, and topical verapamil for PD
  • This does not rule out rehab forever, but evidence is required

• Further studies should be performed, but ROUTINE rehab in ALL patients is not currently justified
You may be Irish…

but you can’t dance your way out of this one!