Penile Rehabilitation Is Beneficial after Pelvic Oncology Surgery

Con Position

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Disclosures

• None
Trinity Is a Shining Star in Sexual Medicine
What Exactly Are We Debating?

**NOT DEBATING:**
- PDE5’s improve erectile function in rats
- Use of PDE5’s improves erectile function while on therapy
- Penile traction / VED improves penile length

**YES DEBATING:**
- Treatment of HUMAN males post pelvic therapy 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
Facetious 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
Levels of Evidence – Oxford Criteria

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Trials Supporting Rehab
Pro Rehab RCT, PC Trials

N=40, Post-RP

2 wks
Sil 50/100 mg qhs
Placebo

8 wks treatment
IIEF 25.2*
IIEF 17.4

14 wks washout?

Results

*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

Sil 50 mg qhs

26%*

IIEF-12.4

36 wks treatment

Sil 100 mg qhs

29%*

IIEF-13.7

8 wks washout

Placebo

4%*

IIEF-8.8

Results

*Response – ≥ 8 on Q3-4 IIEF; p=0.02


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Pro Rehab RCT, PC Trials

Padma-Nathan, et al.\textsuperscript{1}

- Meta-analysis, expected placebo response 34\% (CI 30-38\%)\textsuperscript{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

\textbf{*Response} – ≥ 8 on Q3-4 IIEF; \( p=0.02 \)

Pro Rehab RCT, PC Trials

Montorsi, et al.¹

N=27, Post-RP

4 wks

12 wks treatment

No washout!

Results

Alprostadil 3x/wk

67% spontaneous erections*

Observation

20% spontaneous erections*

*P<0.01

Trials Failing to Support Rehab
Anti Rehab RCT, PC Trials

Montorsi, et al.\(^1\)

\[ \begin{align*}
N=423, \\
Post-RP \\
\text{Var 10 + PC prn} \\
\text{PC qhs + Var 5-20 prn} \\
\text{Placebo} \\
\text{Results} \\
\text{Results} \\
\text{Results} \\
\text{Var prn} \\
\end{align*} \]

*Primary outcome IIEF\(\geq\)22 after washout

Human Studies - RCT

Take Home Points:
1. Biggest RCT
2. **NO** difference after washout
3. **NO** benefit on subsequent prn response

Anti Rehab RCT, PC Trials

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

Primary outcome IIEF ≥ 22 after washout

Take Home Points:
1. **NO** difference after washout
2. **NO** benefit on subsequent prn response
Other Anti Rehab RCT Trials

Pavlovich, et al.¹
- RCT, Sil 50 qhs + Plc prn vs Plc qhs + Sil 50 prn
- Optimal group (≤65 yrs, IIEF≥26, nerve sparing)

Kim, et al.²
- Sil 50 qhs vs Plc
- Prn use permitted

Both 12 mo + 1 mo washout
No true placebo arms

Other Anti Rehab RCT Trials

• No difference in IIEF scores
• No difference in RigiScan scores

What About ICI?

No RCTs

Yiou, et al.¹

• Retrospective, N=75
• Post-RP, good erections pre-op
• ICI beginning 1 mo, twice weekly
• Assessments at 12, 24 months

Results:

• No difference in IIEF w/ or w/o ICI

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
- Pavlovich / Kim (2013, 2016), N=174
How Can We Argue Against the Evidence?

1. Discredit the methods
   
   - Remember, trials were developed by leaders in the field who felt that the protocols were optimal to achieve 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 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. Use anecdotes
   • “Who here does some form of rehab…”

• Comment: follow the $ - are any industry groups applying for new drug indication? Why not?

Trinity Is a Shining Star in Sexual Medicine
What Does Trinity Say About This?

Landmarks in erectile function recovery after radical prostatectomy

Emmanuel Weyne, Fabio Castiglione, Frank Van der Aa, Trinity J. Bivalacqua and Maarten Albersen

Abstract | The description of the nerve-sparing technique of radical prostatectomy by Walsh was one of the major breakthroughs in the surgical treatment of prostate therapy, in animal models. However, most of these approaches have either failed to translate to clinical use or have yet to be studied in human subjects. Penile rehabilitation with PDE5Is is currently the most commonly used clinical strategy, in spite of the absence of solid clinical evidence to support its use.

“Penile rehabilitation with PDE5Is is currently the most commonly used clinical strategy, in spite of the absence of solid clinical evidence to support its use.”
What Does Trinity Say About This?

A large double-blind prospective randomized trial (REINVENT) fails to show the effectiveness of daily administration of vardenafil as a treatment for ED after nerve-sparing radical prostatectomy.

FK506 and GPI-1046 fail to show proven benefit in erectile function recovery after nerve-sparing radical prostatectomy in humans.

A large double-blind prospective randomized trial (REACTT) fails to show the effectiveness of daily administration of tadalafil as a treatment for ED after nerve-sparing radical prostatectomy when compared with on-demand use and placebo.

First phase I safety data for penile injection of bone-marrow mononucleated cells in humans.

ALL large RCTs demonstrate PDE5I failure!!!
The Data Are Clear:

- PDE5s do NOT work – if you offer them, you’re recommending an expensive placebo
- Inadequate evidence to suggest ANY therapy other than potentially VED or PTT to maintain / improve length

The ONLY Role for Penile Rehab:

- Clinical trial - experimental

Soapbox:
As a society, we should be leading the charge to educate those on the data, not holding to untenable positions
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”

• Not saying to not treat ED, but we’re not doing true “Rehab”
At the End of the Day, Which Cochran(e) Do You Choose to Be?
Thank You