The New Business of ED therapy
Understanding Emerging Therapies for ED

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Disclosures (COI)

Grants

• NIH
• CIACT
• SMSNA

Consultant

• Pfizer
• Lilly
“It takes 50 years to get a wrong idea out of medicine and 100 years to get a right one into it”

John Hughlings Jackson
Neurologist
Sexual Activity

• Pfeiffer et al. Arch Gen Psych. 19:735, 1968.
  - 95% of men 46-50 years had sex weekly
  - 28% of men 66-71 years

• The Janus Report (1993)
  - 83% of men 39-50 years had sex weekly
  - 68% of women of same had weekly sex

• Charleston Heart Study Cohort (1995)
  - 40% of 80 year old having regular sexual activity

• Braun et al. IJIR. 12:305, 2000
  - 71% of 70-80 year olds were having sex
  - 41% of 70-80 year olds were having sex weekly

• Lindau et al, NEJM 2008
  - 50% of men >70 years sexually active
  - 30% of women >70 years sexually active
Prevalence of Erectile Dysfunction

Massachusetts Male Aging Study (N=1290)
Men aged 40 to 70 years

No erectile dysfunction (48%)  Erectile dysfunction (52%)

Complete (10%)
Moderate (25%)
Minimal (17%)

Source: Erectile Dysfunction Monograph (1998)
## Prevalence of ED: Worldwide Results

<table>
<thead>
<tr>
<th>Population</th>
<th>Age (y)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cologne, Germany</td>
<td>30-80</td>
<td>19.2</td>
</tr>
<tr>
<td>Iberian Peninsula, Spain</td>
<td>25-70</td>
<td>18.9</td>
</tr>
<tr>
<td>Perth, Australia</td>
<td>40-69</td>
<td>33.9</td>
</tr>
<tr>
<td>Krimpen, Netherlands</td>
<td>50-78</td>
<td>11.0</td>
</tr>
<tr>
<td>London, UK</td>
<td>16-78</td>
<td>19.0</td>
</tr>
</tbody>
</table>

Predicted Increase in ED Prevalence
2025

Worldwide prevalence will increase from 152 million men in 1995 to 322 million men by 2025.

North America: 9.1 million increase
South/Central America and Caribbean: 15.6 million increase
Europe: 11.9 million increase
Africa: 19.3 million increase
Asia: 113 million increase
Oceania: 0.9 million increase

Organic Causes of ED

- 40% Vascular
- 30% Diabetes
- 15% Medication
- 6% Pelvic surgery, radiation, or trauma
- 5% Neurological causes
- 3% Endocrine problems
- 1% Other
# Process of Care Model

<table>
<thead>
<tr>
<th>First-line therapy</th>
<th>Second-line therapy</th>
<th>Third-line therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lifestyle modification</td>
<td>• Intracavernosal injections</td>
<td>• Penile implants</td>
</tr>
<tr>
<td>• Medication adjustment</td>
<td>• Intraurethral alprostadil</td>
<td>• Vascular reconstruction</td>
</tr>
<tr>
<td>• Psychology input</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Oral agents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vacuum devices</td>
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<td></td>
</tr>
</tbody>
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Pathophysiology of Severe ED

- Endothelial Damage
- Neural Injury
- Smooth Muscle Damage
Background

• ED often irreversible in certain populations

• Some patients struggle to respond to oral therapies

• Intracavernosal injections unpalatable to many

• Patient population becoming more savvy

• “New business of ED therapy”
Need for New Strategies

• Fear of current therapies
• Failure
• Contraindications
• Dissatisfaction
• Patients seeking a cure
Emerging Therapies for ED

• Novel pharmacotherapy
• Shock wave therapy
• Stem cell therapy
• Gene therapy
• Platelet rich plasma
• Perineural therapeutics
• Endovascular stenting
The New Business of ED Therapy

• Acquire a small amount of animal or experimental data

• Conduct under-powered studies with flawed end-points

• Engage a small number of clinicians to advocate

• Generate patient interest and demand

• Develop an attractive business model for clinicians

• The therapy becomes “accepted” as off-label
Novel Pharmacotherapy
Ideal (Oral) Agent

• Excellent safety profile (Tissue selectivity)

• Effective (Tissue selectivity)

• Low cost (Industry, Market)

• Rapid onset of action (Drug delivery/formulation)

• Good duration of action (Drug formulation)

• Minimal food/drug interaction (Drug delivery/formulation)
Combination Therapy

• Hypertension management as a template
• Synergistic pathways
• Adverse event profile
• Multi-modal therapy
• Data supporting combining PDE5i (C5 QD + “booster”)
• Data supporting combination of PDE5i/MUSE
• Viable option in the future
Personalized Therapy

• Cause-specific therapy: comorbidity and genomics profile

• Understanding the individual’s sexual dynamics
  - Frequency
  - Predictability
  - Integratability

• Facilitating flexibility for the patient/couple through possession of multiple different strategies in his sexual armamentarium (PDE5i, ICI, MUSE, VED)
Novel Erectogenic Agents

• New PDE5i (oral)
  - Udenafil (Zydena)

• Soluble guanylate cyclase activators (oral)
  - BAY-60-4552 (Phase I/II trials – combined with Var)

• ROCK inhibitors (systemic administration)
  - Y-27632 (pre-clinical)
  - SAR-407899 (early phase human trials)
• Robust data supporting mesenchymal stem cells (MSC) and adipose tissue derived (ADSC) stem cells in improving erectile function in a number of animal models
  - Aging
  - Diabetes
  - Cavernous nerve injury

• No efficacy or safety trial has been reported in humans
Stem Cell Therapy

• 7 trials (NCT02087397, 012398370, 02344849, 01601353, 02240823, 01953523, 02472431)
  - 2 industry sponsored
  - 2 university hospital-based
  - 3 private clinician-initiated) are registered

• One of these is closed (feasibility study in 8 patients), one is not recruiting yet and the remaining 5 are enrolling. 5/7 studies are clearly feasibility studies with enrollment targets <30
Stem Cell Therapy

- Google search for “stem cell therapy, erectile dysfunction” (accessed August 8, 2015) = 309,000 hits

- Centers around the world offering intracavernosal stem cell therapy as a treatment for ED for cash payment

- Charges = $6000-10,000 for each injection of stem cells
This is a fantastic clinic! Dr. [redacted] helped me tremendously with ED issues arising from a radical prostatectomy performed in 2008. During 2015, Dr. [redacted] and his staff administered stem cell therapy and two rounds of rich platelet plasma therapy. The procedures were instrumental in helping me regain function. I strongly advise anyone with ED issues arising from prostate gland surgery to consult with him to determine if he can help you like he did me.
Shock Wave Therapy (SWT)
Extracorporeal Cardiac Shock Wave Therapy Markedly Ameliorates Ischemia-Induced Myocardial Dysfunction in Pigs in Vivo
Takahiro Nishida, Hiroaki Shimokawa, Keiji Oi, Hideki Tatewaki, Toyokazu Uwatoku, Kohtaro Abe, Yasuharu Matsumoto, Noriyoshi Kajihara, Masataka Eto, Takehisa Matsuda, Hisataka Yasui, Akira Takeshita and Kenji Sunagawa

_Circulation_. 2004;110:3055-3061; originally published online November 1, 2004; doi: 10.1161/01.CIR.0000148849.51177.97
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Comparative analysis of angiogenic gene expression in normal and impaired wound healing in diabetic mice: effects of extracorporeal shock wave therapy

Stephen R. Zins · Mihret F. Amare · Douglas K. Tadaki · Eric. A. Elster · Thomas A. Davis

Extracorporeal Shock Wave Therapy (ESWT) Minimizes Ischemic Tissue Necrosis Irrespective of Application Time and Promotes Tissue Revascularization by Stimulating Angiogenesis

Rainer Mittermayr, MD,*† Joachim Hartinger,* Vlado Antonic, MS,§§ Alexandra Meini, PhD,*¶ Sabine Pfeifer,* Alexander Stojadinovic, MD,§§# Wolfgang Schaden, MD,† and Heinz Redl, PhD*


Extracorporeal Shock Wave Therapy Reverses Ischemia-Related Left Ventricular Dysfunction and Remodeling: Molecular-Cellular and Functional Assessment

Morgan Fu19, Cheuk-Kwan Sun2,3,9, Yu-Chun Lin1,4, Ching-Jen Wang5, Chiang-Jen Wu1, Sheung-Fat Ko6, Sarah Chua1, Jiunn-Jye Sheu1, Chiang-Hua Chiang6, Pei-Lin Shao9, Steve Leu1,4, Hon-Kan Yip1,4

Received February 18, 2011; Accepted August 9, 2011; Published September 6, 2011
Study 1 (Vardi): Non-RCT in PDE5i responders

Study 2 (Vardi): Non-RCT in PDE5i failures

Study 3 (Vardi): RCT in PDE5i responders

Study 4 (Olsen): RCT in general ED population
SWT Study 3: Vardi et al

- ED ≥ 6 months
- PDE5i responder with EFD score ≥ 19
- PDE5i hiatus for 1 month before and during study
Study Design

**Baseline assessment**
(IIEF, QEQ, SEAR, RS, NPT and FMD)

**Follow-up Assessments**
(IIEF, QEQ, SEAR, EDITS, RS, NPT and FMD)

- Treatment sessions x2/w
- No Treatment
- Treatment sessions x2/w
- Final Treatment

Weeks:
1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 22, 36
Results

- Change in EFD score = 6.7 (3.0 for sham group)
- 65% had ≥5 point improvement (20% sham group)
- 68% had EHS ≥3 (none in sham group)
SWT Study 4: Olsen et al

• Olsen et al from a RCT study of 112 patients over 24 weeks showed there were improvements at 5 weeks in 57% but this later dropped to 19% at 24 weeks follow-up

• 21 studies registered (NCT02412345, NCT02152683, NCT02422277, NCT02304679)
  - 4 active
  - 7 no longer recruiting
  - 2 terminated
  - 8 unknown status
SWT: Limitations

• Absence of patient characterization (duplex Doppler US)
• IIEF is a poor definition of organicity of ED
• Sex diaries are a requirement in modern ED trials
• Short-term assessment (Vardi Study 3)
• EFD score changes
• Sample size
• Single center
• Dosing strategy
• Drop-out assessment
• Absence of adverse event assessment
• Google search for “shock wave therapy, erectile dysfunction” on August 8, 2015 produced = 81,300 hits

• Several centers offering this as an off-label treatment with prices ranging from $2000-5000 cash
Option 1: Six Treatment Special
This is the most popular option and what we typically suggest. The equipment manufacturer also suggests a 6 treatment protocol.

$2350

Option 2: Five Treatments with option to add Sixth
Though we suggest most people complete Six treatments, some studies show good result with 5 treatments. You can start with 5, then depending how you are feeling, can purchase the 6th at your discretion.

$2020 First 5 treatments
$395 Sixth treatment if requested

Option 3: Six treatments with Split payments
For a small premium, you can split the payments of a 6 treatment plan.

$1250 at first treatment
$1175 at fourth treatment

Option 4: Pay as you Go
We offer this for flexibility. We do however still suggest you complete Six Treatments total.

$495 first treatment
$400 subsequent treatments
Platelet Rich Plasma (PRP)
PRP

• Some potential in the orthopedic literature
• Created by extracting platelet-rich fraction from blood
• Injecting it into the injured body part (ICI)
• Based on idea platelets stimulate growth factors
• Cochrane review on PRP therapy studies for treatment of musculoskeletal injuries found no significant difference in treatments groups versus controls
• 3 studies in China and Taiwan utilizing PRP in a cavernous nerve injury rat model (positive)
PRP

• Google search for “PRP, erectile dysfunction” on August 8, 2015 produced 75,300 hits = 38,000

• Among the claims websites marketing this treatment are making include “bigger erections, improved your sex life, improvement in climax/orgasm, increased sensitivity, increased libido” and “improves sensation even years after prostatectomy.”

• Approximately 228 available providers are listed in the directory for the Priapus shot® (USA), which is a trademark for the PRP injection process

• The PRP injection procedure costs between $1500 - $3000 cash per injection.
The NEW Process of Care Model

• First-line therapy
  - Remove modifiable factors
  - Psychological support
  - Oral therapy
  - Combination Therapy
  - Cause-specific therapy

• Second-line therapy
  - Transurethral agents
  - Intracavernosal injection therapy
  - VED
  - Stem cell therapy
  - Gene therapy
  - SWT

• Third-line therapy
  - Vascular surgery
  - Penile prosthesis insertion
The New Business Model

• Develop ‘sexy’ treatment strategy
• Engage willing KOLs to promote it (them)
• Design sub-par trials
• Generate data not rigorous enough for FDA
• ‘Publish’ the data
• Attract patients focused on novel technology (and not real data)
• Give KOLs/engaged specialists office based technology
• Charge for disposables
• Treatment becomes “accepted’
Take Home Messages

• There is need for novel therapies in the prostate cancer population
• Your patients will know about these
• Early data are intriguing (SWT, Stem cell therapy)
• Great opportunity to conduct robust animal studies
• Need phase I/II studies
• Adequately powered, multicenter phase III trials will be needed

• The greatest concern is the apparent attempt to rapidly commercialize the therapy without adequate data
CREATE NEW PASSWORD?

'PENIS'

SORRY - YOUR PASSWORD ISN'T LONG ENOUGH