Scientific and Clinical Rationale
Erectile dysfunction is a global issue projected to affect 332 million people by 2025.

- China: 134.0 million
- U.S.: 38.4 million
- Brazil: 34.4 million
- Germany: 14.0 million
- France: 8.0 million
- UK: 11.7 million
- Spain: 4.3 million
- Italy: 2.9 million

Junior, 2002; Zhag, 2017; Hallanzy, 2019; Giullinano, 2002; McKinlay, 2000; Kessler, 2017

*Reporting by market may vary based on survey methodology, willingness to admit sexual issues, age distribution of population, etc.*
Erectile dysfunction is exceedingly common, affecting 35-40 million male Americans. Risk factors include coronary heart disease, diabetes and COPD.

- Hypertension in males (000): 33.1 million
- Diabetes in males: 15.3 million
- Chronic bronchitis & emphysema in males: 4.8 million

ERECTILE DYSFUNCTION IS ASSOCIATED WITH AGING, CHRONIC DISEASES, MEDICATIONS AND BEHAVIORAL HEALTH

ED ASSOCIATIONS

• Age
  • Hypertension
• Cardiovascular disease
  • Coronary artery disease, stroke, peripheral vascular disease
• Depression
• Diabetes
• Neurological disease
  • Parkinson’s Disease, Multiple Sclerosis
• Medications for hypertension, diabetes, etc.
• Psychological factors (10-20% of cases)
  • Post-surgical complications
  • Radical prostatectomy, TURP

DIABETES AND ERECTILE DYSFUNCTION

• 30.3 million Americans have diabetes; 9.4% population and 25.2% seniors. Approximately 1.5 million new cases per year

• “In the Massachusetts Male Aging Study, diabetic men showed a threefold probability of having ED when compared to men without diabetes; moreover, the age-adjusted risk of ED doubled in diabetic men when compared to those without diabetes.

• The occurrence of ED is 10–15 years earlier in men with diabetes; moreover, ED is more severe and less responsive to oral drugs in diabetes, leading to reduced quality of life.”

ED FACTOIDS

- Approximately one-third of American males age 35-74 have moderate-to-complete ED (25.5 million)
- An estimated 12% seek physician treatment from a urologist (3.1 million)
- According to the AUA, there are 226 ED subspecialists (1.8% of total), estimated to account for 10.6% of ED patient visits
- Within the generalist urologist physician pool are physicians who focus on male reproductive health issues
INITIAL TARGETING TO BE DRIVEN BY CLINICAL DATA AND FOCUSED ON ED SPECIALISTS

### U.S.

<table>
<thead>
<tr>
<th>Year of launch</th>
<th>t=1</th>
<th>t=2</th>
<th>t=3</th>
<th>t=4</th>
<th>t=5</th>
<th>t=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male population: 35-74 years x % ED</td>
<td>77,461</td>
<td>77,855</td>
<td>78,249</td>
<td>78,643</td>
<td>79,037</td>
<td>79,429</td>
</tr>
<tr>
<td>= ED population (000)</td>
<td>40,215</td>
<td>40,447</td>
<td>40,679</td>
<td>40,911</td>
<td>41,143</td>
<td>41,373</td>
</tr>
<tr>
<td>ED population moderate-to-complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>19,658</td>
<td>19,771</td>
<td>19,884</td>
<td>19,997</td>
<td>20,110</td>
<td>20,225</td>
</tr>
<tr>
<td>Complete</td>
<td>5,839</td>
<td>5,883</td>
<td>5,927</td>
<td>5,971</td>
<td>6,015</td>
<td>6,057</td>
</tr>
<tr>
<td>ED target population</td>
<td>25,497</td>
<td>25,654</td>
<td>25,811</td>
<td>25,968</td>
<td>26,125</td>
<td>26,282</td>
</tr>
<tr>
<td>% ED population 35-74</td>
<td>32.9%</td>
<td>33.0%</td>
<td>33.0%</td>
<td>33.0%</td>
<td>33.1%</td>
<td>33.1%</td>
</tr>
<tr>
<td>Physician referrals: Patients seeking treatment (000)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6%</td>
<td>1179</td>
<td>1186</td>
<td>1193</td>
<td>1200</td>
<td>1207</td>
<td>1214</td>
</tr>
<tr>
<td>9%</td>
<td>2,295</td>
<td>2,309</td>
<td>2,323</td>
<td>2,337</td>
<td>2,351</td>
<td>2,365</td>
</tr>
<tr>
<td>12%</td>
<td>3,060</td>
<td>3,078</td>
<td>3,097</td>
<td>3,116</td>
<td>3,135</td>
<td>3,154</td>
</tr>
<tr>
<td>15%</td>
<td>3,825</td>
<td>3,848</td>
<td>3,872</td>
<td>3,895</td>
<td>3,919</td>
<td>3,942</td>
</tr>
<tr>
<td>Specialist concentration</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of urologists</td>
<td>226</td>
<td>12,291</td>
<td>12,517</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x ED patients/week</td>
<td>30.0</td>
<td>4.6</td>
<td>5.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients/week</td>
<td>6,780</td>
<td>56,981</td>
<td>63,761</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>x 48 weeks/year</td>
<td>48</td>
<td>48</td>
<td>48</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED patients/year</td>
<td>325,440</td>
<td>2,735,092</td>
<td>3,060,532</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Alternative treatment modalities may be inappropriate, ineffective or associated with adverse events

<table>
<thead>
<tr>
<th>Oral</th>
<th>Topical or Non-invasive</th>
<th>Injectable or Implant</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE5-inhibitors (70% effectiveness)</td>
<td>Topical alprostadil</td>
<td>Intra-cavernosal injections</td>
</tr>
<tr>
<td></td>
<td>intra-urethral (IU) alprostadil</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vacuum devices</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low-intensity shock-wave</td>
<td>Inflatable penile prosthesis (25,000/annum)</td>
</tr>
</tbody>
</table>

Note: Intra-cavernous injections may include phentolamine, papaverine, and alprostadil. It's an invasive procedure that is associated with dropout rates as high as 40%–50% due to pain, priapism, penile fibrosis, hematoma, ecchymosis, or fear of the needle.
First line of treatment, PDE-5 inhibitors, do NOT meet the needs of all patients (and are contraindicated in angina, heart attack and uncontrolled hypertension).

### Efficacy: Successful intercourse for general ED population

- **Sildenafil (Viagra)**: EFFICACY: 69%
  - Recommended dose: 50mg, 1 hour before sexual activity, may be adjusted to 100mg or 25mg
  - Bioavailability: 41%
  - Time to peak plasma levels: 60 minutes
  - Half-life: 3-5 hours
  - Onset of action: 25 minutes
  - Duration of action: up to 4 hours
  - Food: high-fat meals delay the time to peak plasma concentration by 60 mins and reduce peak plasma levels by 29%
  - Common side effects: headache, dizziness, flushing, nasal congestion, nausea, dyspepsia, visual abnormalities

- **Vardenafil (Levitra)**: EFFICACY: 71-80%
  - Recommended dose: 10mg, 25-60 minutes before sexual activity, may be adjusted to 20mg or 5mg (film-coated only)
  - Bioavailability: 15%, (film-coated), 19% (microdispensible)
  - Time to peak plasma levels: 60 minutes (film-coated), 45-90 minutes (microdispensible)
  - Half-life: 4-5 hours
  - Onset of action: 25 minutes
  - Duration of action: up to 12 hours
  - Food: high-fat meals delay the time to peak plasma concentration by 60 mins (film-coated) and reduce peak plasma levels by 20% (film-coated) or 35% (microdispensible)
  - Common side effects: headache, dizziness, flushing, nasal congestion, dyspepsia. Inhibits PDE6, which can cause transient visual abnormalities. Can prolong QTc interval

- **Avanafil**: EFFICACY: 47-59%
  - Recommended dose: 100mg, 15 to 30 minutes before sexual activity, may be adjusted to 200mg or 60mg
  - Bioavailability: not determined
  - Time to peak plasma levels: 30-45 mins
  - Half-life: 6-7 hours
  - Onset of action: 15-30 minutes
  - Duration of action: up to 6 hours
  - Food: high-fat meals delay the time to peak plasma concentration by 75 mins and reduce peak plasma levels by 39%
  - Common side effects: headache, flushing, nasal congestion

- **Tadalafil (Cialis)**: EFFICACY: 75%
  - Recommended dose: 10mg, 30 minutes before sexual activity, may be adjusted to 20mg or 25-50mg daily
  - Bioavailability: not determined
  - Time to peak plasma levels: 120 minutes
  - Half-life: 17.5 hours
  - Onset of action: 15-30 minutes
  - Duration of action: up to 36 hours
  - Food: rate and extent of absorption are not influenced by food
  - Common side effects: headache, flushing, nasal congestion, dyspepsia, myalgia and back pain

**PDE-5 Inhibitors Are Not Suitable for All Patients:**

- **Levitra (Vardenafil)**: Suitable for patients with cardiovascular disease and diabetes
- **Cialis (Tadalafil)**: Suitable for patients with liver disease
- **Viagra (Sildenafil)**: Suitable for patients with renal impairment

Efficacy: Successful intercourse for general ED population

https://www.pharmaceutical-journal.com/download?ac=1072931
Second- and third-line product offerings may impact intimacy, result in local adverse events or be invasive

<table>
<thead>
<tr>
<th>First-line</th>
<th>Efficacy</th>
<th>Impact on intimacy</th>
<th>Functional recovery period</th>
<th>Immediacy of effect</th>
<th>Sustainability of effect</th>
<th>Adherence</th>
<th>Safety</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDE5 inhibitors</td>
<td>70%</td>
<td>Low</td>
<td>NA</td>
<td>15-30 minutes</td>
<td>4-36 hours</td>
<td>NA</td>
<td>systemic side effects; drug interactions. Contra-indicated CV disease</td>
<td>$25-60/pill x 40 pills/year = $1,000-2,400/annum</td>
</tr>
<tr>
<td>Second-line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical alprostadil</td>
<td>39-75%</td>
<td>Moderate</td>
<td>NA</td>
<td>5-30 minutes</td>
<td>1 hour</td>
<td>Dose titration often required</td>
<td>Local burning, pain erythema; resolve 2 hours</td>
<td></td>
</tr>
<tr>
<td>intra-urethral (IU) alprostadil (suppository)</td>
<td>68%</td>
<td>Moderate</td>
<td>NA</td>
<td>5-20 minutes</td>
<td>1 hour</td>
<td>Dose titration may be required</td>
<td>Penile pain (36%), urethral burning and pain (13%), erythema, bleeding</td>
<td>$66/suppository</td>
</tr>
<tr>
<td>Vacuum devices</td>
<td>50-80%</td>
<td>High</td>
<td>NA</td>
<td>2-3 minutes</td>
<td>30 minutes</td>
<td>Difficult in obese men; need coordination</td>
<td>Numbness, pain, bruising, painful ejaculation; unnatural feeling</td>
<td>$300-500/unit</td>
</tr>
<tr>
<td>Low-intensity shock-wave</td>
<td>60-65% in patient subsets</td>
<td>None</td>
<td>4-16 weeks?</td>
<td>Spontaneous</td>
<td>No standard protocol (6-12 applications x 1-2/week) +/- break</td>
<td>+/- painful during administration</td>
<td>$2,500-6,000; platelet rich plasma extra</td>
<td></td>
</tr>
<tr>
<td>MyoStim ED</td>
<td>70-80%</td>
<td>None</td>
<td>4-8 weeks</td>
<td>Spontaneous</td>
<td>&gt;6 months</td>
<td>Two 45 minute office visits per week x 4-8 weeks</td>
<td>No side effects</td>
<td>$1,600</td>
</tr>
<tr>
<td>Third-line</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-cavernosal injections</td>
<td>94%</td>
<td>High</td>
<td>2 session injection training</td>
<td>5-15 minutes</td>
<td>&lt;2-4 hours</td>
<td>Penile injection required</td>
<td>wrong injection site, trauma, fibrosis, priapism</td>
<td>$3-6/dose, syringes</td>
</tr>
<tr>
<td>Inflatable penile prosthesis (IPP)</td>
<td>80-90%</td>
<td>Moderate</td>
<td>2-4 weeks</td>
<td>NA</td>
<td>Manual controls</td>
<td>Permanent</td>
<td>Infection, bleeding, scar tissue</td>
<td>$20-30,000</td>
</tr>
</tbody>
</table>

1 Based on patient selection criteria; 2 Pending FDA approval; 3 FDA status unclear
**Limitations and adverse events of erectile dysfunction (ED) treatment with phosphodiesterase type 5 (PDE5) inhibitors**

<table>
<thead>
<tr>
<th>Limitation</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic side effects</td>
<td>• Headache</td>
</tr>
<tr>
<td></td>
<td>• Visual disturbance</td>
</tr>
<tr>
<td></td>
<td>• Priapism</td>
</tr>
<tr>
<td></td>
<td>• Flushing</td>
</tr>
<tr>
<td></td>
<td>• Muscular pain</td>
</tr>
<tr>
<td></td>
<td>• Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>• Sinus congestion</td>
</tr>
<tr>
<td>Drug interactions</td>
<td>• Variable efficacy as a result of increased/decreased PDE5 inhibitor plasma concentration</td>
</tr>
<tr>
<td>• Inhibitors/inducers of P-450*</td>
<td>• Enhanced variable efficacy</td>
</tr>
<tr>
<td>• Antihypertensive agents</td>
<td>• Severe hypotension</td>
</tr>
<tr>
<td>• Alpha-blockers **</td>
<td></td>
</tr>
<tr>
<td>• Nitrites</td>
<td></td>
</tr>
<tr>
<td>Decreased absorption with fatty meals</td>
<td>• Decreased efficacy</td>
</tr>
<tr>
<td></td>
<td>• Loss of spontaneity</td>
</tr>
</tbody>
</table>

**Notes:**

* Cytochrome P-450 inhibitors;
**alpha-blockers are used for the treatment of hypertension and benign prostatic hyperplasia.
Erectile dysfunction is very common, especially in the rapidly aging population with co-morbid cardiovascular disease and diabetes.

Patient preferences are integral to product selection and the trade-off between satisfaction and adverse events.

Unmet needs are global and remain despite the presence of several treatments (algorithms) in the U.S. and Europe; PDE-5 inhibitors as first line therapy and a range of topicals, devices and procedures as second line therapy.

Myostim represents a potentially significant and differentiated entrant targeting the pathophysiology of erectile dysfunction with proprietary signals.
Figure 1. There are morphological and physiological mechanisms involved in the process of aging that play a key role in the development of sexual dysfunction. Cardiovascular risk factors and hypogonadism have a critical impact during the establishment of the aging process that could also lead to erectile dysfunction. Cellular senescence could induce oxidative stress and hence inflammation that with time leads to accumulative damage. With this overview, the main mechanisms of the aging process that drive toward erectile dysfunction include vascular and physiologic alterations and penile morphologic changes.
• Bioelectrical stimulation (BES) is applied clinically for treating a variety of disorders, such as wound healing.
• BES is based on safely modulating various electrical signals to stimulate or inhibit the expression of specific key genes, to counteract the known molecular pathophysiology of ED and not just induce vasodilation.
• Effects may potentially repair for a long-term solution: vasculature, pressure (vasoconstriction/dilation balance), nerves and penile corporal histopathology.
• The first ED treatment to not just address temporary blood flow improvement but to treat muscle and nerve damage recovery.
Proprietary precise bioelectric signaling affects local physiology

- SDF-1 for stem cell homing
- IGF-1 for DNA repair
- Follistatin for muscle repair
- eNOS for dilating blood vessels
- VEGF, PDGF, EGF, HIF1a, CXCL5 and SDF1

DNA REPAIR AND ANTI-AGING

Klotho
The regeneration of smooth muscle cavernosa by BES should result in the spontaneous return of erectile in contrast to the oral, injection therapy and the use of a vacuum pump where the patient is treatment dependent.

- **Klotho**: the secretory Klotho results in the reduction in TNFα and IFNγ, which can show anti-inflammatory properties. Klotho can interact with Wnt, which results in the inhibition of Wnt pathway activity, thus inhibiting the aging process.
- **IGF-1**: improve nerve regeneration and neuromuscular recovery.
- **Follistatin**: promotes muscle regeneration and recovery. Follistatin is able to accomplish accelerated muscle restoration not only by leveraging the regenerative effects of myostatin inhibition but potentially through modulating inflammation.

5. Journal of Pharmacology and Experimental Therapeutics · March 2014 DOI: 10.1124/jpet.113.211169

*Potentially curative, though sustainability of effect requires determination*
**Research Communication**

**Vol. 170, No. 2, 1990**

**BIOCHEMICAL AND BIOPHYSICAL**

**July 31, 1990**

**Pages 843-850**

**NITRIC OXIDE AND CYCLIC GMP FORMATION UPON ELECTRICAL FIELD STIMULATION CAUSE RELAXATION OF CORPUS Cavernosum SMOOTH MUSCLE**

Louis O. Ignarro, Peggy A. Bush, Georgette M. Buga, Keith S. Wood, Jon M. Fukuto and Jacob Raff*  

Department of Pharmacology and Division of Urology, *Department of Surgery University of California, Los Angeles, CA 90024

Received June 18, 1990

**SUMMARY:** In the presence of functional adrenergic and cholinergic blockade, electrical field stimulation causes corpus cavernosum smooth muscle by unknown mechanisms. We report here that electrical field stimulation of isolated strips of rabbit corpus cavernosum promotes the endogenous formation and release of nitric oxide (NO), nitrite, and cyclic GMP. Corporal smooth muscle relaxation in response to electrical field stimulation in the presence of

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**The Effect of Treatment of Erectile Dysfunction with Electrical Stimulation**

Myung-Chool Gil, Yun-Chul Oh, Ta-Woo Kang and Gyung-Woo Jung

*From the Department of Urology and the Institute of Andrology, Dong-A University, Pusan, Korea*

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**Free paper**

**Functional electromyostimulation of the corpus cavernosum penis – preliminary results of a novel therapeutic option for erectile dysfunction**

C. G. Stief1, E. Wellershof, T. Noack1, M. Djamilian1, M. Mesch1, M. Truss1, and U. Jonas1

1Department of Urology, Medizinische Hochschule Hannover, D-30623 Hannover, Germany  
2Department of Physical Medicine and Rehabilitation, Medizinische Hochschule Hannover, D-30623 Hannover, Germany  
3Department of Physiology, University of Marburg, Marburg, Germany
PD28-03
EFFECTS OF FUNCTIONAL ELECTROSTIMULATION ON ERECTILE FUNCTION RECOVERY FOLLOWING BILATERAL NERVE-SPARING RADICAL PROSTATECTOMY: A RANDOMIZED SHAM-CONTROLLED STUDY

Anna Paula Braga*, Scheila Nascimento, Roberto Soler, Sao Paulo, Brazil

INTRODUCTION AND OBJECTIVES: To evaluate the effect of functional electrostimulation (FES) as a penile rehabilitation procedure on the erectile function (EF) of patients following nerve sparing radical prostatectomy (NSRP).

METHODS: This was a prospective, blind, randomized, sham-controlled trial. The study included men ≤70 yr undergoing radical prostatectomy with bilateral preservation of the neurovascular bundle, with previous unassisted normal EF (International Index of Erectile Function, Erectile Function domain IIEF-EF score ≥26), total PSA < 10 ng/mL and Gleason score ≤7. Patients were randomly assigned, in a 1:1 ratio, to undergo FES or sham procedure. Penile rehabilitation was performed for 6 months, twice a week, during 30 minutes. Patients were evaluated at 1, 3, 6, 9 and 12 months after the start of the procedures. The primary endpoint was the proportion of patients with IIEF-EF score ≥22 after 12 months of the start of treatment. Secondary endpoints included rate of positive responses to Sexual Encounter Profile (SEP) questions 2 and 3 and to Global Assessment Question (GAQ) questions 1 and 2.

RESULTS: Twenty and three patients were randomized to FES and 26 to sham. After 12 months of the start of the study procedures 52.2% and 19.2% of patients reached IIEF-EF score ≥22 in FES and sham groups, respectively (p = 0.016). This effect was also observed in other endpoints (table 1). A significantly higher proportion of patients in FES group compared to sham group had positive responses to SEP2 and GAQ1 from the 6th month to the end of the study. There was numerical, but no statistical, difference in the rate of SEP3 and GAQ2 positive responses between the groups. No adverse events related to FES were reported by patients.

CONCLUSIONS: Functional electrostimulation was efficacious and safe as a penile rehabilitation procedure in improving recovery of unassisted EF in patients undergoing NSRP. The effect of FES was maintained after cessation of active therapy.

Table 1 – Proportion of patients with IIEF-EF ≥22 according to treatment group

<table>
<thead>
<tr>
<th>Month</th>
<th>Treatment</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FES (n=23)</td>
<td>EFS (n=26)</td>
<td>P</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16.7%</td>
<td>11.8%</td>
<td>1.002</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>38.1%</td>
<td>4.0%</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>45.5%</td>
<td>15.4%</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>47.6%</td>
<td>19.2%</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>52.2%</td>
<td>19.2%</td>
<td>0.016</td>
<td></td>
</tr>
</tbody>
</table>

Source of Funding: Coordination for the Improvement of Higher Education Personnel (CAPES)
An initial study on the effect of functional electrical stimulation in erectile dysfunction: a randomized controlled trial

Cristiane Carboni 1, Alexandre Fornari 1, Karoline C. Bragante 1, Marcio A. Averbeck 1, Patrícia Vianna da Rosa 1, Rodrigo Della Mea Plentz 1

Received: 7 April 2015 / Revised: 27 December 2017 / Accepted: 12 February 2018 / Published online: 22 May 2018 © Macmillan Publishers Limited, part of Springer Nature 2018

Abstract
Erectile dysfunction (ED) affects approximately 150 million men worldwide. Functional electrical stimulation (FES) therapy has shown a high regenerative capacity for smooth muscle cells and, therefore, is being increasingly adopted. FES can be a beneficial treatment option when the cause of ED is related to degeneration of cavernous smooth muscle. To evaluate the
MYOSTIM ED CLINICAL TRIALS
MYOSTIM ED II CLINICAL TRIALS
UMPUBLISH DATA
Erection Hardness Score

p < 0.001

Percent Change (%)

Untreated

MyoStim ED Signals
MyoStim ED II study results

Recovery of Morning Erection

- Untreated: 10%
- MyoStim ED Signals: 89%

Recovery of Penis Enlargement

- Untreated: 0%
- MyoStim ED Signals: 89%

$p = 0.001$ and $p < 0.001$
Blood Flow + Muscle + Nerve Regeneration. We have the Only Complete ED Solution addressing ALL Causes

HOWARD LEONHARDT, CEO
SHOCK WAVE THERAPY: ED CURE OR UNPROVEN TREATMENT?

- American Urological Association: “investigational” (2018); Sexual Medicine Society of North America “experimental, for use under research protocols” (March 2019)
- Poorly designed clinical studies precludes generalizability of results: different treatment protocols (application frequency and duration, therapy duration), inclusion/exclusion criteria, types of devices (# shock waves, energy level). Clinical end-points, etc.*
- Pooling of data (n=873) suggests improvement in vasculogenic patients.\textsuperscript{2} Registry trial planned by GAINSWave
  - Expensive $3-6,000 for treatment
  - Unclear patient selection criteria
  - Off-label use in “packages” with platelet rich plasma and other adjunctive technologies (e.g., vacuum pumps)
  - Targets vasculogenic source of ED i.e., atheromatous plaque destruction and not neovascularization, tissue regrowth, etc.
  - Device offerings from Storz Medical (Cellator), Zimmer (Z-wave), Eclipse Medical (Evive), Direx and others
  - Use by unscrupulous clinic, spa and chiropractic clinics

Urology Times; August 6, 2019; Int J Impot Res 2019 May;31(3):177-194
MyoSTIM ED

U.S. Business Model

Physician imprimatur (brand equity)

- Physician office application
- Physician sale to patient for personal use
- OTC device designation (DTC)

Urologists (12,660)¹
ED subspecialists (226)
GP/FP/IM (160,000)²

¹file:///C:/Users/grube/Downloads/2018%20The%20State%20of%20Urology%20Workforce%20Census%20Book.pdf
127k Myostim patients – 4.2% of the referral population - at $1,600 per patient ($200 per treatment) generates >$200m in U.S. high margin practice revenues.

*Revenues also generated from premium device sales to urologists and professional sale of “basic” device to patients. Excludes use of Myostim as commercially available consumer product. European ED market (patients) > U.S. > Brazil. China has 3-4x number of ED patients as compared to the U.S.
Investment Spending

<table>
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<tr>
<td>Total</td>
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Treatment algorithms established by AUA and European Associated of Urology based on severity of ED, outcomes, adverse events and satisfaction. Patient preferences noted.

**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.

**IF INADEQUATE EFFICACY AND/OR UNACCEPTABLE AEs AND/OR INSUFFICIENT SATISFACTION, THEN ADDRESS AS APPROPRIATE:**
- Dose adjustments (for PDE5i, IU alprostadil, ICI).
- 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.

1 For men with testosterone deficiency, defined as the presence of symptoms and signs and a total testosterone <200 ng/dl, counseling should emphasize that restoration of testosterone levels to therapeutic levels is likely to increase efficacy of ED treatments other than prosthesis surgery.

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Erectile dysfunction market development exceeding 30 years!

THREE DECADES OF VIAGRA

Sildenafil (Viagra) – the first oral drug for erectile dysfunction to hit the market in 1998 – has been prescribed for more than 64 million men worldwide, and may soon be reclassified as a pharmacy medicine in the UK.

BY DAWN CONNELLY & ALISDAIR MACDONALD

Sildenafil, a drug that selectively targets and powerfully inhibits the enzyme phosphodiesterase type 5 (PDE5), is first synthesised and tested in Pfizer’s UK laboratories.
The first trial of sildenafil for coronary heart disease shows it is ineffective but penile erection is noticed as a side effect.
Sildenafil (Viagra, PDE5i) is approved by the US Food and Drug Administration (FDA) in March and the European Medicines Agency (EMA) in September as the first oral treatment for men with ED.

DRUG APPROVALS AND MARKET DEVELOPMENTS

Sildenafil showed promise as an oral treatment for erectile dysfunction (ED) in the early 1990s and was launched by Pfizer as Viagra in 1998. Since then, three more PDE5 inhibitors have been launched in the UK. Sildenafil events are shown on the top of the timeline and other PDE5 inhibitor events are below the line.

Tadalafil (Cialis, Eli Lilly) is approved for the treatment of ED by the EMA in November, and by the US FDA in November the following year.

37.0m
By 2008, Viagra had been prescribed for more than 37 million men worldwide

2008
Pfizer withdraws an application to the EMA to market Viagra over the counter for ED after the regulator expresses concerns that there would be no medical supervision, which could delay diagnosis of possible cardiovascular disease.

64.0m
By 2016, Viagra had been prescribed for more than 64 million men worldwide

2016
Boots becomes the first UK pharmacy to offer Viagra without prescription under a patient group direction.

5.4bn
5.4 billion Viagra tablets had been dispensed worldwide by 2016

2016
Tesco breaks into the Viagra market and offers the drug to customers without a prescription under a patient group direction.

The UK patent on Viagra expires, opening the way for generic versions of sildenafil to be launched.

Generic sildenafil can now be prescribed on the NHS for any male with ED, whereas previously it was restricted to those with ED because of an underlying health condition, such as diabetes or prostate cancer.

The Medicines and Healthcare products Regulatory Agency (MHRA) recommends sildenafil 50mg (Pfizer) should be available as a pharmacy medicine, and launches a consultation that closes in April.


Vardenafil (Levitra; Bayer) is approved by the EMA for the treatment of ED in March and the US FDA in August.

The European Commission approves low-dose (2.5mg and 5.0mg) tadalafil as single-daily ED therapy.

Vardenafil (10mg) is the first PDE5 inhibitor introduced for ED in an odourless tablet.

Avanafil (Spedra, Vivanza) is approved for treatment of ED by the US FDA in April and by the EMA in June 2013.

Manufacturer of Cialis, Lilly, agrees a deal with Sanoﬁ to allow the French firm to buy exclusive rights to apply to sell Cialis as a non-prescription medicine in Europe, the United States, Canada and Australia after certain patents expire.

Vacuum devices are effective in 50-80% of patients but have side effects and other possible drawbacks.

**Side effects**

Side effects of using a penis pump can include:

- **Pinpoint-sized red dots (petechiae).** This is caused by bleeding under the surface of the skin of the penis.
- **Numbness, coldness or bluish-colored skin.** This can occur when the constriction band is in place.
- **Pain or bruising.** Knowing how to use the penis pump correctly can help you avoid injury to your penis.
- **Feeling of trapped semen.** You might feel like your semen is trapped when you ejaculate, or ejaculation might be painful. Some manufacturers make constriction rings with a small cutout that might help with this.

Penis pumps have some other possible drawbacks:

- **Unnatural-feeling erections.** Penis pumps can cause an erection that doesn’t feel natural or spontaneous. You might have a lack of firmness at the base of the penis, which can allow the penis to rotate or pivot more than it would with a natural erection.
- **Awkwardness.** Use of a penis pump requires patience and understanding from both you and your partner. It might take some time to become comfortable with the device.
- **Manual coordination is required.** Penis pumps require use of the hands and fingers to operate, which can be a problem for some men or their partners.

[https://www.mayoclinic.org/tests-procedures/penis-pump/about/pac-20385225](https://www.mayoclinic.org/tests-procedures/penis-pump/about/pac-20385225)
Shockwave therapies are effective in 60-65% of patients at one month; treatment is expensive and inconvenient ($3,000 \times 10-12$ sessions). It is NOT FDA approved for this indication.

The researchers found that at one month, treatment was successful in 99 patients (63.5%), but during follow-up a gradual decrease in efficacy was observed. At 2 years, the beneficial effect was maintained in only 53.5% of patients in whom success was initially achieved. Over follow-up the treatment effect was lost in all patients with diabetes who initially had severe erectile dysfunction. However, for patients with milder forms of erectile dysfunction without diabetes there was a 76% chance that the beneficial effect of low-intensity shock wave treatment would be preserved after 2 years.
Although erectile dysfunction does not present risks to the individual's life, it can provoke a series of disorders, such as decreased self-esteem, increased anxiety, social relationship impairment and depression, among others. Such disorders may cause repercussions on the general health of the patient.

This is the reason why our team worked in the Complete Solution for ED.
LEONHARDT'S LAUNCHPADS
BY CAL-X STARS
12655 W Jefferson Blvd, Los Angeles, CA 90066

LEONHARDT'S LAUNCHPADS UTAH, INC
370 S, 300 E, Salt Lake City, UT 84111

EMAIL ADDRESS
hleonhardt@aol.com

CONTACT INFORMATION