Low Energy Shockwaves for the Treatment of Erectile Dysfunction

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Haifa, Israel
Shock waves - principles

Generated by electro-hydraulic effect:

- High voltage creates electric spark discharge
- The water vaporizes and creates an explosion generating shock waves
- Reflected by the Semi-Ellipsoid
- Focused onto the treatment area
Shockwave Applications

- Lithotripsy
- Stone Fragmentation
- Anti-inflammatory
- Angiogenesis
- Orthopedics
- Cardiology
- ED

Shock Wave Pressure Level (Bar)

- 1970's
- 1980's
- 2000's
- 2010
Proposed Mechanism of Action- angiogenesis

- Shockwaves are successfully used globally since 2005 to treat reversible coronary ischemia, by inducing angiogenesis/neovascularization and developing new collaterals, resulting in increased tissue perfusion.

- The same modality can be used for treating vascular-based Erectile Dysfunction.
Can we improve the erectile mechanism?

Prof Y Vardi set up a research team which included Dr Boaz Appel and Omar Massarwa. Together with Medispec who had the ED1000 adapted for this research.

Can we reverse erectile dysfunction?
Current drug therapies have limitations

- On-Demand (Timing dependent, time dependent)
- Lack of spontaneity
- Total dependence on therapy
- Treatment and not cure
- Bothersome adverse events from PDE5i
- Contraindication to PDE5i

  - Limited effectiveness:
  - >50% of responders are not fully satisfied with their sex lives
  - 50% discontinue treatment
There are unmet needs with the current treatment of sexual dysfunction
A significant revolution in the treatment of ED in the past 15 years

“LI-ESWT is the only treatment dealing with the cause of ED, and not with the symptoms”
From theory to practice- how is it done?

Control panel
Shockwave generator
Shockwave applicator (SWA)

Dimensions: height: 740 mm x width: 775 mm x depth: 410 mm
Applying Shockwaves to the Penile shaft

1. Stretch the penis.
2. Firmly attach the shockwave applicator to the treatment location using water-based gel
3. Apply 300 shocks at three locations across the shaft (below the gland and above the base)
Applying Shockwaves to the Crura

1. Locate the pubic bone of the patient.
2. Deliver 300 shocks beneath the pubic bone with the SWA center toward the crus as indicated on the picture.
Low Energy Shock Waves for Erectile Dysfunction

Shaft

Crura
Treatment protocol

Week 1

Week 2

Week 3

3 weeks
Treatment protocol

Week 1

Week 2

Week 3

3 weeks

6 weeks

NO TREATMENT
Treatment protocol

Week 1 | Week 2 | Week 3

3 weeks

NO TREATMENT

Week 7 | Week 8 | Week 9

6 weeks

9 weeks

Treatment is non-invasive, painless and without side-effects!!!
Study Design

Screening

1m Wash out

52 weeks
Study Design

Baseline assessment
Evaluation with validated questionnaires and hemodynamic assessment.

Screening

1m Wash out

52 weeks
Study Design

Screening

Baseline assessment
- Visit 1: Evaluation with IIEF, QEQ, RS, SEARS, FMD.

1m Wash out

3 w Treatment | 3 w Interval | 3 w Treatment

52 weeks

9 weeks treatment
Study Design

Screening

Baseline assessment
Visit 1: Evaluation with IIEF, QEQ, RS, SEARS, FMD.

1m Wash out

3 w Treatment
3 w interval
3 w Treatment

9 weeks treatment

End term Evaluation

1m no treatment

Follow-up assessment
F.U 1: Evaluation with IIEF, QEQ, RS, SEARS, EDITS, FMD.

52 weeks
Study Design

Baseline assessment
Visit 1: Evaluation with IIEF, QEQ, EHS, SEARS, FMD.

Screening
1m Wash out
3 w Treatment
3 w Interval
9 weeks treatment
3 w Treatment

End term Evaluation
52 weeks
1m no treatment

Follow-up assessment
F.U 1: Evaluation with IIEF, QEQ, EHS, SEARS, EDITS, FMD.

F.U 2: 3m Evaluation IIEF-ED Domain
F.U 3: 6m Evaluation IIEF-ED Domain

F.U 2: 3m Evaluation IIEF-ED Domain
F.U 3: 6m Evaluation IIEF-ED Domain
Subjective assessment:
THE IIEF - EF DOMAIN SCORE

<table>
<thead>
<tr>
<th>IIEF-EF Domain Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>Normal (≥26)</td>
</tr>
<tr>
<td>25</td>
<td>Mild (22-25)</td>
</tr>
<tr>
<td>20</td>
<td>Mild to Moderate (17-21)</td>
</tr>
<tr>
<td>15</td>
<td>Moderate (11-16)</td>
</tr>
<tr>
<td>10</td>
<td>Severe (&lt;10)</td>
</tr>
</tbody>
</table>

Increase in the IIEF EF in more than 5 points = real effect

MCID-minimal Increase in the IIEF EF such that the patient feels an effect


Increase in the IIEF EF in more than 5 points = real effect
# Defining Success

## MCID

<table>
<thead>
<tr>
<th>Change from baseline to week 12</th>
<th>Development sample (n = 863)</th>
<th>Validation sample (n = 377)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>Minimum</td>
</tr>
<tr>
<td>IIEF EF domain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No change in Q7/MMI (n = 679)</td>
<td>1.27 (5.48)</td>
<td>-15</td>
</tr>
<tr>
<td>Minimal improvement in Q7/MMI (n = 184)</td>
<td>7.27 (5.93)</td>
<td>-7</td>
</tr>
</tbody>
</table>

| ANOVA-based MCID ¹ | 7.27 (6.46-8.07) | <0.001 | -     | -     | -     | -     |

### ROC-based MCID by ED severity level ³

<table>
<thead>
<tr>
<th>Severity</th>
<th>MCID</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>2</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
</tr>
<tr>
<td>Severe</td>
<td>7</td>
</tr>
</tbody>
</table>

¹ Important difference; Q7/MMI = question 7 measure of minimal improvement; ROC = receiver operating characteristic; SD = standard deviation.

² The p value tests the interaction of the ED severity level by Q7/MMI in predicting the change from baseline to week 12 of the IIEF EF domain of the analysis of covariance model.

³ The p value tests the significance of the association between the IIEF Q7/MMI and the dichotomy of the EF domain and was calculated using logistic regression.

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**Minimal Clinically Important Differences in the Erectile Function Domain of the International Index of Erectile Function Scale**

Raymond C. Rosen ⁴, Kerstin R. Allen ⁴, Xiao Ni ⁵, Andre B. Araujo ⁴

⁴ New England Research Institutes, Inc., Watertown, MA, USA; ⁵ Eli Lilly USA, LLC, Indianapolis, IN, USA
ERECTION HARDNESS SCORE (EHS)

Severe ED
IIEF < 10

Moderate ED
IIEF 11 - 15

Mild ED
IIEF 16 - 20

No ED
IIEF > 20

1. Penis is larger but not hard

2. Penis is hard but not hard enough for penetration

3. Penis is hard enough for penetration but not completely hard

4. Penis is completely hard and fully rigid

Evaluating Subjective treatment Success

CGIC: 1 Question
SEP: 5 Questions
Objective Assessment:
Endothelial Dysfunction measurement by Flow Mediated Dilatation technique
The flow-mediated dilatation technique - a new clinical method for the assessment of penile endothelial function

Y Vardi & al J Urol 2005
Does it work?
Pilot Study-PDE5i responders

• 20 patients with diabetes and/or cardiovascular history

• Mean age 56.1±10.7y,

• Average IIEF-EF domain scores 13.5 and abnormal NPT.

• Agreed to stop PDE5i treatment during all study protocol
Pilot Study Design

Baseline assessment
Without PDE5i

Follow-up assessment
Without PDE5i

1m Wash out
3 w Treatment X2/w (Total =6)
3 w no treatment
3 w Treatment X2/w (Total =6)
1m no treatment

F.U 2: 3m
Evaluation IIEF-ED Domain

F.U 3: 6m

52 weeks
## Results

<table>
<thead>
<tr>
<th>Test</th>
<th>Baseline</th>
<th>1 month F.U.</th>
<th>%</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>IIEF EF Domain</td>
<td>13.5</td>
<td>4.1</td>
<td>20.6</td>
<td>5.8</td>
</tr>
<tr>
<td>IIEF Total</td>
<td>39.3</td>
<td>8.7</td>
<td>53.8</td>
<td>11.7</td>
</tr>
<tr>
<td>QEQ</td>
<td>34.6</td>
<td>18.2</td>
<td>65.2</td>
<td>25.8</td>
</tr>
<tr>
<td>Rigid Score</td>
<td>1.45</td>
<td>1</td>
<td>2.8</td>
<td>1.1</td>
</tr>
<tr>
<td>SEARQ</td>
<td>36</td>
<td>10.4</td>
<td>46.5</td>
<td>11.3</td>
</tr>
</tbody>
</table>

No pain or any other side effects were noted nor reported.
Results - FMD

- Flow (ml/min/dL)

**Penis**

- Basic flow
- Maximal flow

- Baseline
- 1 month F.U.

*p < 0.001*
Overall Results:

- 5 subjects did not respond to the treatment protocol
- In 15 patients - improvement of >5 points
- In 7 of them - improvement of >10 points.

10 patients stopped PDE5i Treatment

5 use it occasionally
First publication (2010)

58/2 August 2010 issue of European Urology

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Sexual Medicine

Can Low-Intensity Extracorporeal Shockwave Therapy Improve Erectile Function? A 6-Month Follow-up Pilot Study in Patients with Organic Erectile Dysfunction

Yoram Vardi *, Boaz Appel, Giris Jacob, Omar Massarwi, Ilan Gruenwald

Neuro-Urology Unit, Rambam Healthcare Campus and the Technion, Haifa, Israel
Is it better than placebo?

Sexual Function/Infertility

Does Low Intensity Extracorporeal Shock Wave Therapy Have a Physiological Effect on Erectile Function? Short-Term Results of a Randomized, Double-Blind, Sham Controlled Study

Yoram Vardi,*† Boaz Appel, Amichai Kilchevsky and Ilan Gruenwald

*From the Urost-Urology Unit, Rambam Healthcare Campus, and the Rappaport Faculty of Medicine, Technion – IIT, Haifa, Israel (YV, BA, AK, IG) and the Department of Urology, Yale-New Haven Hospital, New Haven, Connecticut (IA)
Study Methodology-RPCDB

Randomization

1 month
Washout

Baseline
assessment

1m
22
36

End of
Treatment

Post
treatment

Follow-up
assessment

TREATMENT

SHAM CONTROL

1 month
no treatment

3 w
Treatment
X2/w
(Total =6)

3 w
no
Treatment

3 w
Treatment
X2/w
(Total =6)

Shockwave treatment

(Failures)

Follow up only

(Success)

Extended shockwave treatment

0 1m 1 2 3 4 5 6 7 8 9 1m 22 36

21 weeks

Extension 6m
ED1000 Double Blind Study

RESULTS

IIEF EF Domain scores before and after treatment in both groups

65% improved by more than 5 points in the IIEF-EF)
Success according to erection hardness score (EHS) of ≥ 3

![Bar chart showing success rates in Sham (N=20) and Treatment (N=40) groups.]

- Sham (N=20): N=8 V1, N=7 FU1
- Treatment (N=40): N=12 V1, N=31 FU1
Changes in maximal penile blood flow

![Graph showing changes in maximal penile blood flow with Treated and Placebo groups, indicating a statistically significant difference (P<0.001).]
Changes in IIEF-EF domain scores after treating the placebo group

<table>
<thead>
<tr>
<th>Domain</th>
<th>Baseline</th>
<th>Post-treatment</th>
<th>Extension treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>11.8 ± 1.9</td>
<td>12.8 ± 1.9</td>
<td>16.6 ± 1.2</td>
</tr>
</tbody>
</table>

--- ns --- p = 0.007 --- p = 0.001 ---
Is there any effect in PDE5i NON-responders?

Low-Intensity Extracorporeal Shock Wave Therapy—A Novel Effective Treatment for Erectile Dysfunction in Severe ED Patients Who Respond Poorly to PDE5 Inhibitor Therapy

Ilan Gruenwald, MD, Boaz Appel, MD, and Yoram Vardi, MD
Neuro-urology Unit, Rambam Healthcare Campus, Haifa, Israel
Study Chart

Baseline assessment

Screening Evaluation With PDE5i

Mid term Evaluation

End term Evaluation

Follow-up assessment

F.U 1: Evaluation without PDE5i

F.U 2: Evaluation With PDE5i

Active PDE5i treatment

0 1 2 3 4 5 6 7 8 9 10 11 12 13 17

17 weeks (3 months)
Patients

• 33 non responders entered the study
• 4 Discontinued
• 29 (90.9%) completed 12 weeks
Non-responders: Results

For 22 patients (75.9%) IIEF EF Domain scores changed by 5 points or more once resuming PDE5-I
Changes in Rigidity Scales according to visit

![Bar chart showing the number of patients at each visit according to the Rigidity Scale.]

- Visit 1: 29 patients
  - RS ≥ 3 (Success): 19
  - RS ≤ 2 (Failure): 8
- FU1: 10 patients
  - RS ≥ 3 (Success): 21
  - RS ≤ 2 (Failure): 8
- FU2: 21 patients
  - RS ≥ 3 (Success): 21
  - RS ≤ 2 (Failure): 8

p < 0.001

Non Responders Study Results

- 72.4% of patients **converted** from PDE5i non responders - to responders

- For 75.9% patients IIEF ED Domain scores **change by 5 points and more**
How long does the SW effect last?
Demographics of the Successful group, n=113

• Age: median 58.5, range 27 – 74

• Baseline Severity: Mild (23%), Moderate (44%), Severe (33%)

• Responders to PDE5i: (77%)

• CVRF: (79%)

• CVD: (27%)

• Diabetes: (35%)

• Follow up was performed at 1 m and 3 m in the office and at 6, 12, 18 and 24m by a phone interview.
K-M curve of whole group
time-to-dropout
Two-Years Follow Up in PDE5i responders- MCID Criteria

<table>
<thead>
<tr>
<th>Time Period (Post Last Treatment)</th>
<th>Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Month</td>
<td>100%</td>
</tr>
<tr>
<td>3 Months</td>
<td>72.9%</td>
</tr>
<tr>
<td>6 Months</td>
<td>65.3%</td>
</tr>
<tr>
<td>12 Months</td>
<td>65.3%</td>
</tr>
<tr>
<td>18 Months</td>
<td>61.7%</td>
</tr>
<tr>
<td>24 Months</td>
<td>57.9%</td>
</tr>
</tbody>
</table>
Does an additional series (2nd round) of shock wave therapy improve the results for patients that failed or partly responded to the first round?
Results: 1-month after the 2nd round

- 8/24 (33.3%) had an improvement of $\geq 5$ points in the IIEF-EF
Pooled data analysis
USA FDA Study, Greece, Israel, India and Japan

8 studies assessing safety and efficacy

<table>
<thead>
<tr>
<th>Country</th>
<th># Pts.</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>131</td>
</tr>
<tr>
<td>Greece</td>
<td>46</td>
</tr>
<tr>
<td>Israel</td>
<td>235</td>
</tr>
<tr>
<td>India</td>
<td>135</td>
</tr>
<tr>
<td>Japan</td>
<td>57</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>604</strong></td>
</tr>
</tbody>
</table>

*440 pts. underwent active treatment
Success rate in the group of PDE5i responders

* According to IIEF-EF Domain MCID (Rosen et al., 2011) 298 patients from USA, Greek, India and Israel
Greece: Responders

- Doppler was tested on 46 patients:
  - Treatment group - 30 pts
  - Placebo group - 16 pts

USA: Responders

- The (NPT) was tested on 103 patients
  - Treatment group - 84 pts.
  - Placebo group - 40 pts.
Greece - Individual Plots Describing Maximal Peak Systolic Volume
Safety Results

- Out of 440 patients who participated in 8 studies (US, Israel, Greece, India and Japan):
  - 2 patients have experienced a tingling sensation at the tip of the penis during treatment
  - 1 patient has experienced the sensation of genital burning
  - 1 patient has experienced application site hypersensitivity
  - 2 patients have developed a skin rash due to sensitivity to the application gel

- All the above AEs were self-limited and self-resolved

Treatment with the ED-1000 was well tolerated, reported AE’s were mild and infrequent and support a favorable safety profile
Final remarks and conclusions

Who are the patients who could potentially benefit from LI-ESWT

70% of ED patients may be candidates for LI-ESWT

- Diabetes Mellitus 40%
- Vascular Disease 30%
- Vascular 70%
- Radical Surgery 13%
- Spinal Cord Injury 8%
- Multiple sclerosis 3%
- Endocrine disorders 6%

Graph source: Graham Jackson, Consultant Cardiologist, Guy’s & St Thomas’ Hospital, London, UK.
Treatment Pathway

- Hormones
- Medication: PDE-5 inhibitors
- Vacuum pump
- Injections
- Implants
Meta Analysis* – Success Rates

Patient IIEF-EF Domain

- Severe ED
  - EF Domain ≤ 10 (0-10)
    - Poorly Responders
      - 12 – 24 Tx
      - 62 % Success Rate + PDE5i
    - Responders
      - 12 – 24 Tx
      - 77% Success Rate

- Moderate ED
  - 11 ≤ EF Domain ≤ 21 (11-21)
    - 6 Tx
    - 60-68% Success Rate

- Mild ED
  - 21 ≤ EF Domain ≤ 25 (21-25)
    - 6 Tx
    - 55-64% Success Rate

- Normal ED
  - EF Domain ≥ 26 (26-30)
    - No Treatment

* Internal Meta Analysis
Expectations from SW treatment for ED

• Responders are expected to improve and to be able to perform without PDE5i’s.
• Non Responders are expected to become responders.
Patients that this therapy is not recommended for

- Patients that do not have any erectile response
- Years without any vaginal penetration capability
- Pure Neurogenic patients (MS, Spinal Cord Injury)
- Non responders to Injection therapy
- Post Radical Prostatectomy??
Take Home Messages

• LI-ESWT is the first non-invasive method that has the potential to improve and in some cases even cure the erectile mechanism

• Able to replace oral treatment in patients who previously responded to PDE5i

• Able to reverse PDE5i non-responders to responders

• More data from other centers needed

• More basic science

• A new, even more effective protocol will probably emerge.
Thank you