THE CHAIM SHEBA MEDICAL CENTER
AT TEL HASHOMER
The Hospital of Israel

The 4th Friends of Israel
UROLOGICAL SYMPOSIUM
Tel Aviv, Israel · July 3-5, 2018

LiST for ED
Updatde

Noam D. Kitrey, MD, FECSM

Dept. of urology, Sheba medical center, ISRAEL

Chairman of the EAU UroTrauma guidelines panel

Main points

Data from the last 3-4 years

• How does it work?	Basic science
• Does it work?	Clinical evidence
• For whom?	Target population
• Who’s the enemy?	Misconceptions
• What’s next?	Future research

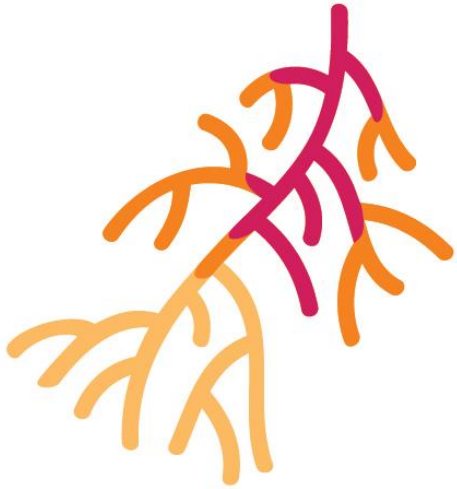
How does it work?

Low-intensity shockwaves mechanism of action

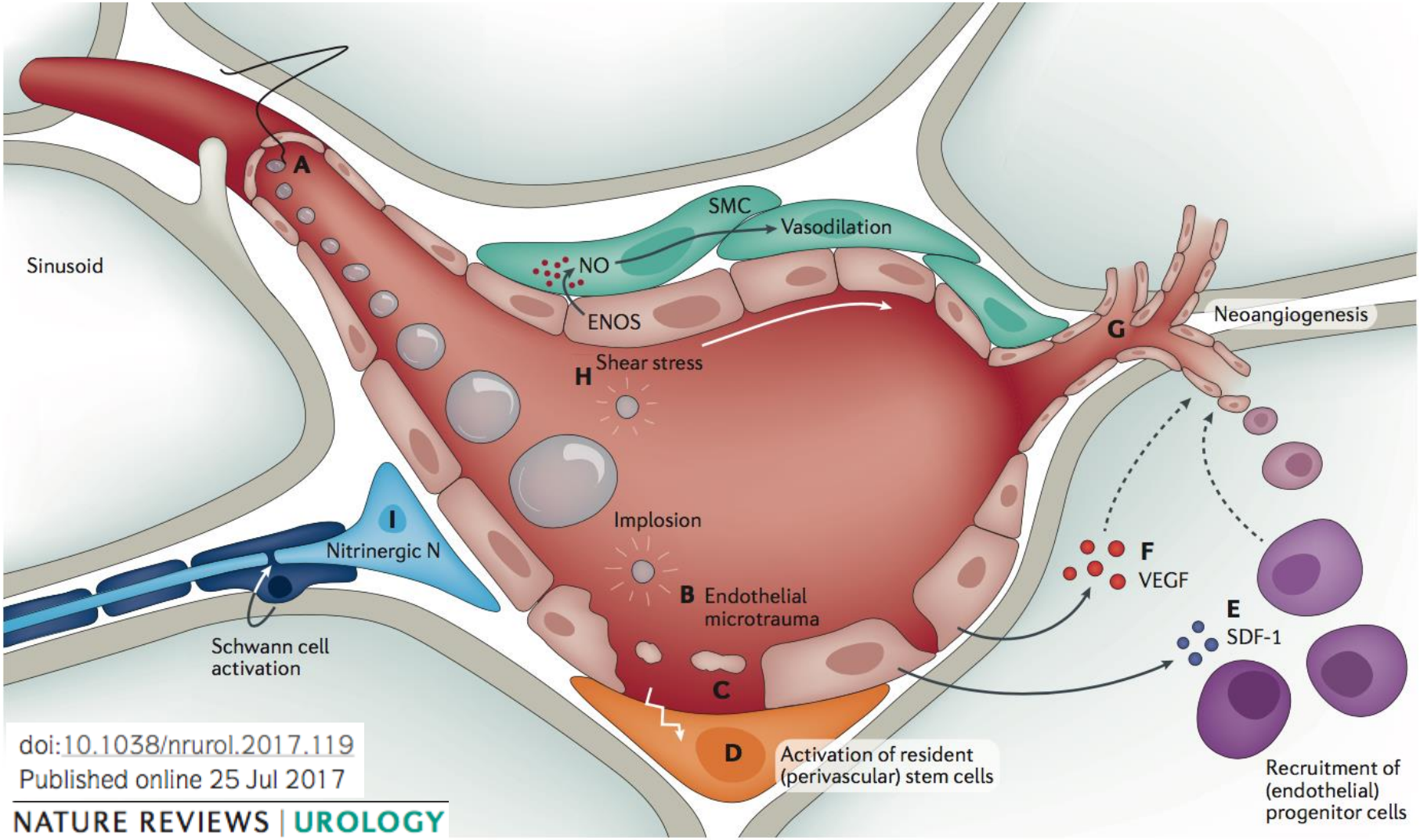
THE HYPOTHESIS

Occlusion of arterioles in the corpora cavernosa

Low-intensity shockwaves initiate the process of angiogenesis

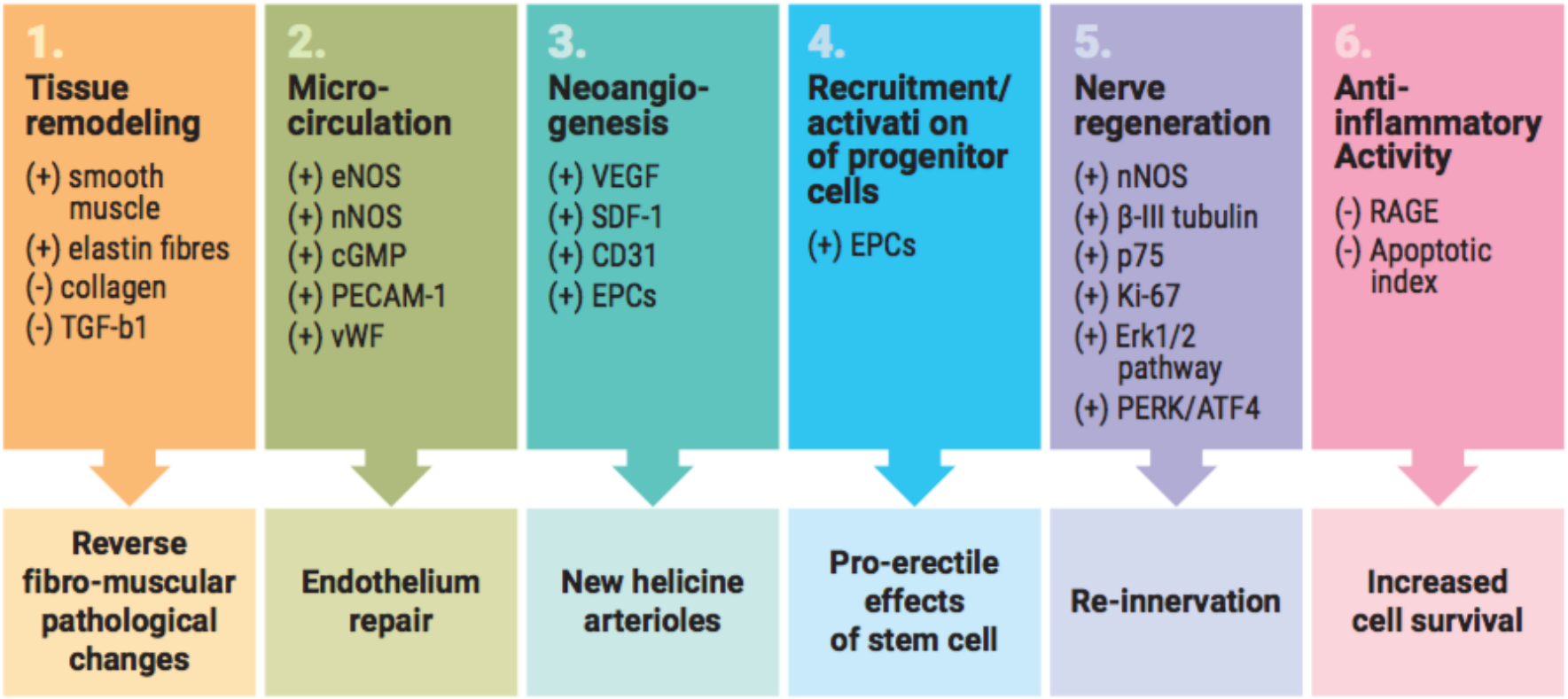


New arterioles lead to improved arterial inflow and better erections



doi:10.1038/nrurol.2017.119
Published online 25 Jul 2017
NATURE REVIEWS | UROLOGY

Low-intensity Shockwaves Therapy (LiST) for Erectile Dysfunction 6 putative mechanisms of action*



*summary on the hypotheses reported on published basic research articles

Animal models for LiST

- Diabetic rats were treated with SW / sildenafil / both
- Acute sildenafil and Li-ST significantly improved erectile responses
- Measured by ICP and AUC/MAP

- Surprisingly, this effect **is not mediated by a NO/cGMP - dependent mechanism**

- The **combination of LiST with sildenafil significantly potentiated the effect** of LiST alone

Assaly-Kaddoum, R, et al: J Urol. 2016;196:950-6

Does it work?

Clinical evidence

2010

Pilot - proof of the concept study

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

Vardi Y et al. 2010 Euro Urol

2012

LiST: first sham-controlled study

THE JOURNAL of UROLOGY®
Official Journal of the American Urological Association

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 Neuro-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 (AK)

Vardi Y et al. 2012 J Urol

2016

LiST is effective in PDE5i non-responders

THE JOURNAL of UROLOGY®
Official Journal of the American Urological Association

Penile Low Intensity Shock Wave Treatment is Able to Shift PDE5i Nonresponders to Responders: A Double-Blind, Sham Controlled Study

Noam D. Kitrey,*,† Ilan Gruenwald,* Boaz Appel,‡ Arik Shechter,* Omar Massarwa* and Yoram Vardi‡

- 54% of the LIST group achieved erection hard enough for vaginal penetration [EHS = 3]
- No patient in the sham group had EHS = 3 ($p < 0.0001$).
- LIST was effective in 40.5% of men treated according to IIEF-EF MCID (Minimal Clinically Important Difference) vs. none in the sham group ($p < 0.001$).

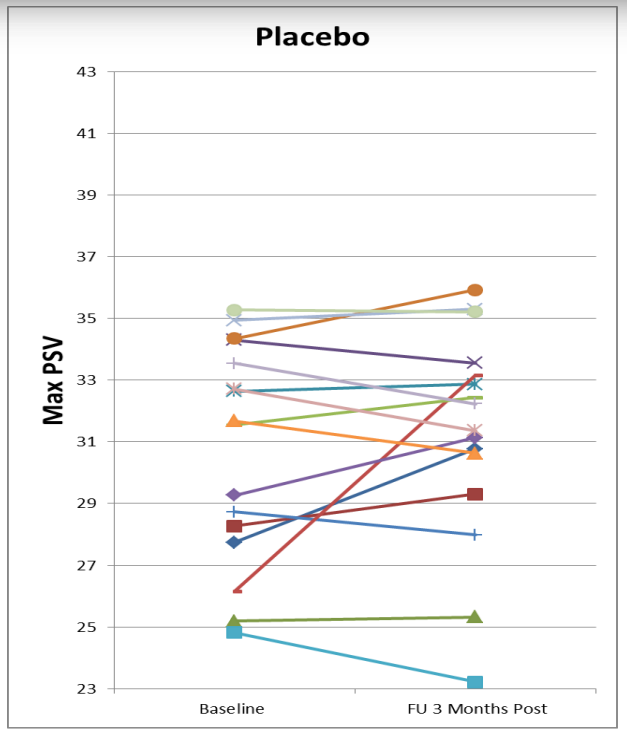
Kitrey ND et al. 2016 J Urol

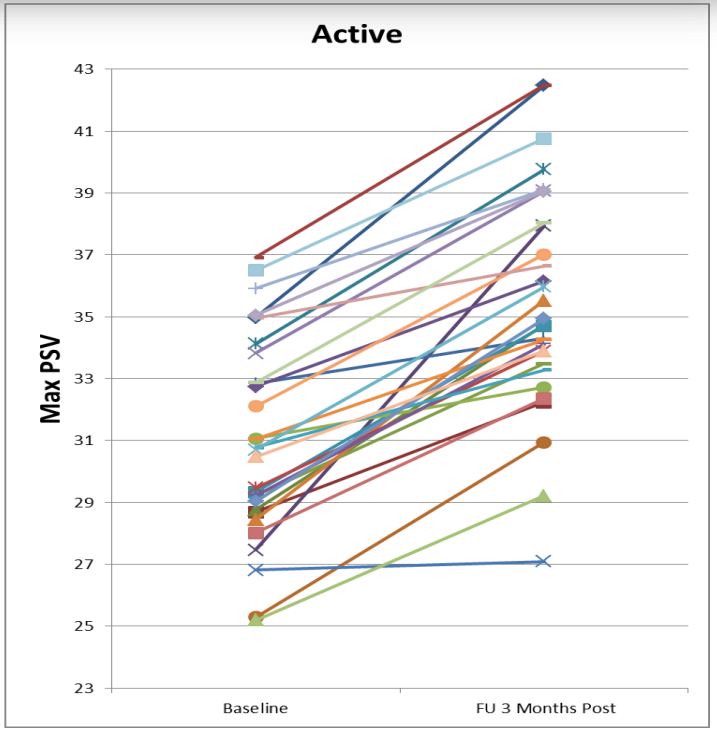
2017

LiST changes penile hemodynamics

Low-Intensity Shockwave Therapy Improves Hemodynamic Parameters in Patients With Vasculogenic Erectile Dysfunction: A Triplex Ultrasonography-Based Sham-Controlled Trial

Dimitrios Kalyvianakis, MD, FECSM, and Dimitrios Hatzichristou, MD, PhD, FECSM





Kalyvianakis D et al. 2017 JSM

2018

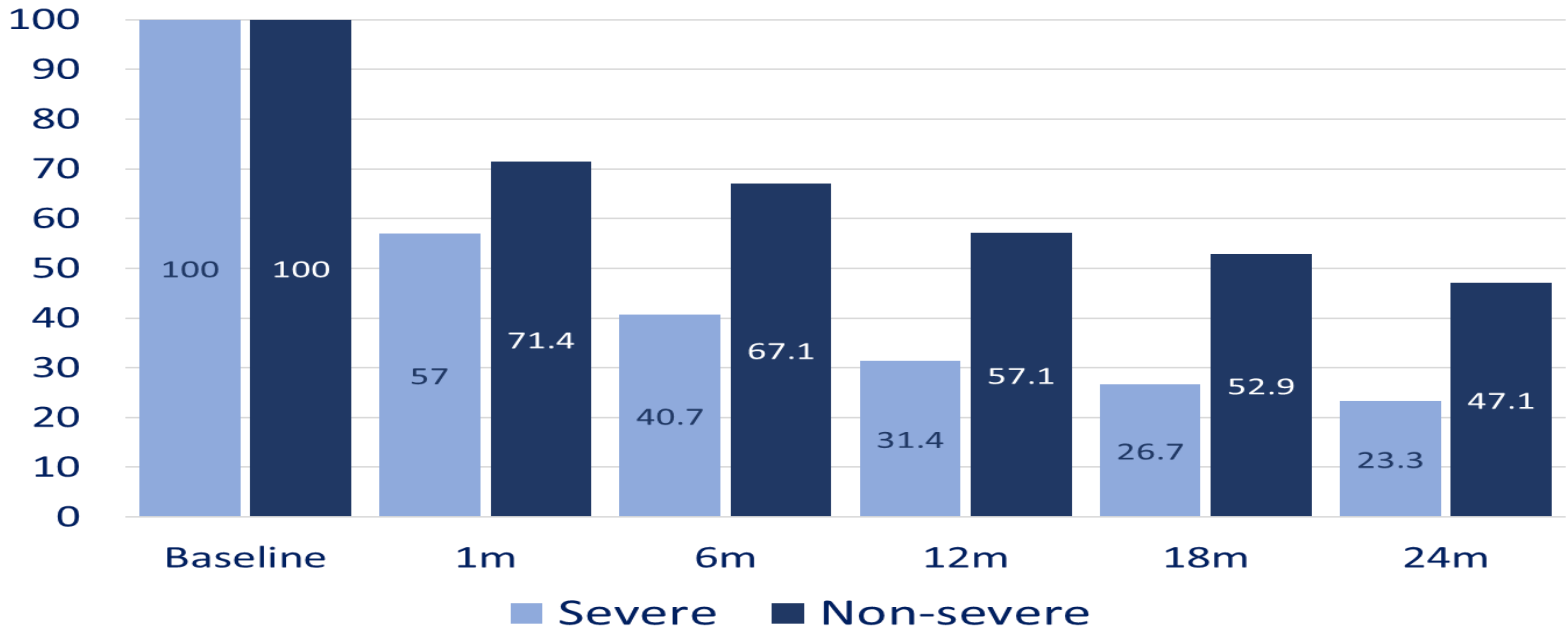
For how long?

Low Intensity Shock Wave Treatment for Erectile Dysfunction—How Long Does the Effect Last?

THE JOURNAL of UROLOGY®
Official Journal of the American Urological Association

Noam D. Kitrey,* Yoram Vardi, Boaz Appel,† Arik Shechter, Omar Massarwi, Yasmin Abu-Ghanem and Ilan Gruenwald

Fig 2: Maintenance of success over time according to ED severity



Kitrey ND et al. 2018 J Urol

2018

For how long?

THE JOURNAL of UROLOGY®
Official Journal of the American Urological Association

Low Intensity Shock Wave Treatment for Erectile Dysfunction—How Long Does the Effect Last?

Noam D. Kitrey,* Yoram Vardi, Boaz Appel,† Arik Shechter, Omar Massarwi, Yasmin Abu-Ghanem and Ilan Gruenwald

- a gradual decrease in efficacy was observed

- Only 53.5% maintained the beneficial effect after two years
- 76% of patients with mild and moderate ED, without diabetes, will preserve the beneficial effect of LIST after two years

Kitrey ND et al. 2018 J Urol

Randomized control trials (n=652 /211 placebo)

	Name	Date	No. of patients	Type of machine	Target population	% success	Journal
1	**Vardi**	2012	60	ED1000 (Medispec)	responders	**58** 3m	J Urol
2	**Yee**	2014	58	ED1000 (Medispec)	mixed	Significant **only in sever** 1 m	Int J Urol
3	**Olsen**	2014	105	Duolit (Storz)	responders	**57** 1 m	Scan J Urol
4	**Sirini**	2015	77	ED1000 (Medispec)	responders	**78** 12 m	Can J Urol **sponsored**
5	**Kitrey**	2016	55	ED1000 (Medispec)	Non-responders	**54** at 3 m	J Urol
6	**Motil**	2016	125	Pyezowave (wolf)		**77** 1 m	Adv Sex Med **sponsored**
7	**Kalyvianakis**	2017	46	ED1000 (Medispec)	responders	**56** 6 m	J Sex Med
8	**Fojecki**	2017	126	Pyezowave (wolf)	mixed	**No effect** 1 m	J Sex Med

1. VardiY: J Urol. Vol. 187, 1769-1775, 2012
2. Yee CH: IntJlUrol21, 1041–1045, 2014
3. Olsen AB: ScandJ Urol, 49(4): 329–333 2014
4. SiriniVS: Can j Urol, 22(1); 2016
5. KitreyND: j Urol:195(5),155015552016
6. MotilI: Advanced sexual Medon line j 2016
7. kalyvianakisD: J Sex Med,14(7):891-897 2017
8. GrzegorzL:J Sex Med ,14:106-112 2017

Published Open labeled studies

	Name	Device	Energy	Sessions	Target population	No. of patients	Success rate
1	**Vardi**	ED 1000 Medispec	Electrohydroulic	12	Responders	20	65%
2	**Reisman**	Direx Renova	Electromagnetic	4	Mixed	58	71%
3	**Pelayo-Nieto**	Direx Renova	Electromagnetic	4	Mixed	15	70%
4	**Gruenwald**	ED 1000 Medispec	Electrohydroulic	12	Non responder	33	62%
5	**Chung -**	Storz Duolith	Electromagnetic	12	Non-responders	30	68%
6	**Frey - Fode**	Storz Duolith	Electromagnetic	6	Post - prostatectomy	16	59%
7	**Ruffo**	Direx Renova	Electromagnetic	4	Non-responders	31	66%
8	**Bechara**	Direx Renova	Electromagnetic	4	Non-Responders	50	48% at 1 year
9	**Tsai**	Storz Duolith	Electromagnetic	12	Non-responders	52	54% 3 m
10	**Kalyvianakis**	Dornier Aries	Electromagnetic	6-12-18	Responders	42	62% (6 sessions) 74% (12 sessions) 83% (18 sessions)

1. VardiY et al (2010) EurUrol
2. ReismanY et al (2014) IntJ ImpotRes
3. Pelayo-Nieto M et al (2015) ActasUrolEsp
4. Gruenwaldl et al 2015 J sex Med
5. Chung E and CartmillR (2015). BJU Int
6. Frey et al (2016) ScandJ Urology
7. RuffoA et al (2015) IntBrasilJ Urol
8. Bacharaet all (2016) J Sex Med
9. Tsai et all (2017) Am J Men Health
10. Kalyvianakis et al (2018) J Sex Med

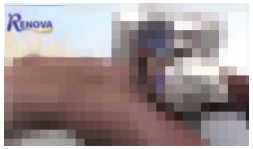
The Market

- **ED 1000** electrohydraulic (Medispec)

- **Urogold 100** electrohydraulic (MTS)

- **Duolith®** SD1 electromagnetic (Storz)

- **Renova** linear SW electromagnetic (Direx)



- **Aries®** electromagnetic (Dornier)

- **PiezoWave2** piezoelectric (Richard Wolf)

	Karl Storz	Dornier	MTS	Medispec	Direx	Richard Wolf
Machine	Duolith SD1	Aries	Urogold100	ED1000	Renova	PiezoWave2
Technology	Electro-magnetic	Electro-magnetic	Electro-hydraulic	Electro-hydraulic	Electro-magnetic	Piezoelectric
Focal zone	Narrow focus	Wide focus	Wide focus (OP155)	Wide focus	Wide focus	Linear focus 46 x 20 x 4mm
Energy penetration depth	0 – 125 mm	0 – 70 mm	0 – 80 mm	0 – 140 mm	0 – 40 mm	0 – 172 mm
Maximum energy flux density	1.25 mJ/mm2	0.31 mJ/mm2	0.19 mJ/mm2 (OP155)	0.09 mJ/mm2	0.09 mJ/mm2	0.82 mJ/mm2
Frequency	1 – 8 Hz	0.5 – 20 Hz	0.5 – 8 Hz	2-2.6 Hz	5 Hz	1-8 Hz
Applicator lifespan	Warranty: 1 M	Warranty: 2 M	100 - 200 K (estimated)	Stops at 180 K	1M (estimated)	Warranty: 5 M
Adjustable buttons on applicator	Yes	Yes	No	Yes (operating & reload)	No	Yes
Applicator weight	770g	500g	850g	1 kg	N.A. (on holder)	0.55 – 1.58

Open questions?

- What is the best protocol, energy parameters, and energy source?
- How to cover better all corporal tissue?
- Who are the suitable patients?
- What are the real outcomes?

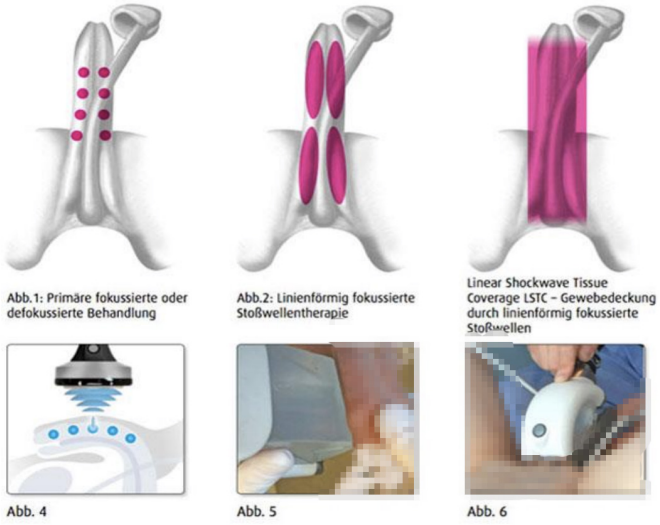
Misconceptions driven by the media and industry!

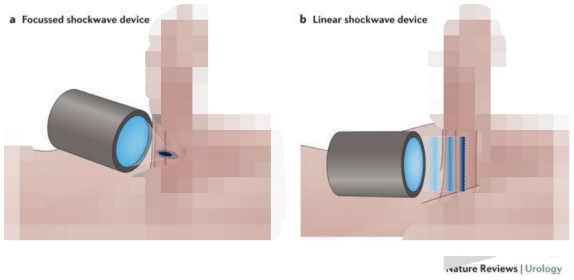
Which treatment parameters?

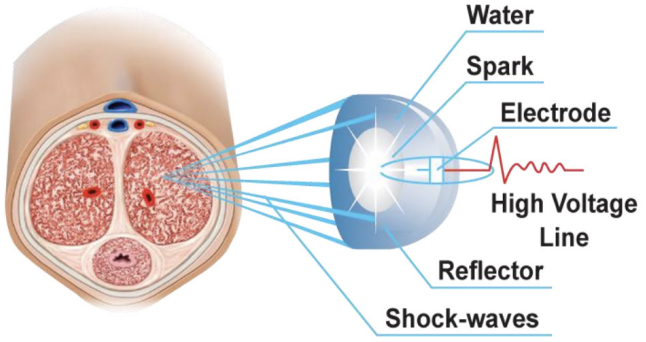
- No data regarding the most effective **energy source**, type of **probe**, and no. of sessions
- Most manufacturers reduce the **no. of sessions** due to patients compliance disregarding efficacy (Between 4 to 12 sessions)
- **Energy flux density** (EFD) 0.09 - 0.25 mJ/mm²
- **Number of shockwave pulses** 1,500 - 6,000
- Is the **break** beneficial?

How to cover better the corpora?

- This is probably the most important issue regarding success
- Every probe and type of energy have a different focus and depth
- The crura are the most tricky part







For whom? Who will not benefit?

- Patients without any **natural erectile response** (lack of tumescence anytime)
- **No response** to PDE5i and injections
- **Post Radical Prostatectomy**?
- Pure **neurogenic ED**?

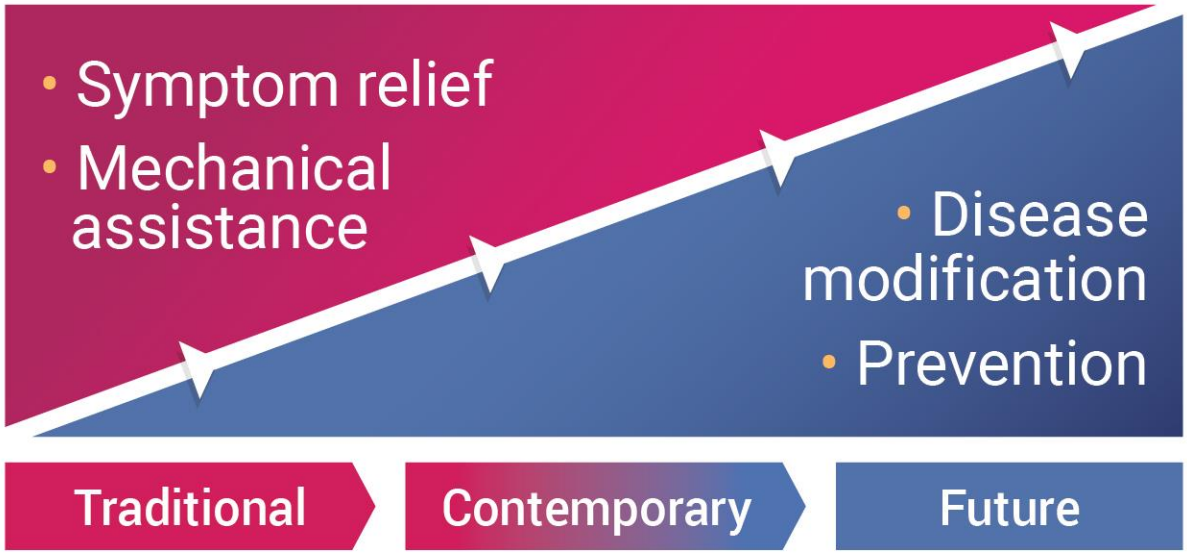
Can we cure ED by LiST?

Probably not

We can **improve** erectile function
in selected patients

With more clinical and basic research the effectiveness of this novel therapy will certainly improve

Shifting the paradigm of ED management



American Urological Association

Erectile Dysfunction: AUA Guideline (2018)

Published 2018

Guideline Statement 24

24. For men with ED, intracavernosal stem cell therapy should be considered investigational. (Conditional Recommendation; Evidence Level: Grade C)

Take Home Messages

- The first non-invasive method that improves erectile mechanism (with moderate results)
- Able to replace oral treatment in patients who previously responded to PDE5i
- Able to shift PDE5i non-responders to responders
- More **BASIC SCIENCE** and **RCT**s are needed
- improved & patient friendly protocol is needed