Focused Ultrasound for the Treatment of Pain

Jessica Foley, PhD
Chief Scientific Officer
Focused Ultrasound Foundation
Chronic Pain

Background

- 40 million US adults
- Over $500 billion annually
- The opioid crisis

How Focused Ultrasound is making a difference

- Non-invasive, non-pharmacologic treatment option
  - Reduces need for opioids
  - No incisions, no risk of infection or bleeding
  - Limited time in hospital (outpatient in some cases)
  - Back to work and daily life quickly
FUS for Chronic Pain

Mechanisms

- Thermal ablation of the nerves surrounding joints and tumors
- Thermal ablation of a small region in the brain that processes pain (thalamus)
- Stimulation or suppression of peripheral nerve signals involved in pain

In 2012, the FDA approved focused ultrasound to treat painful bone metastasis.

In 2012 and 2013, focused ultrasound gained European approval to treat chronic low back pain, neuropathic pain and osteoid osteoma.

Other indications under investigation:

- Osteoarthritis
- Painful stump neuroma
- Peripheral neuropathy
What is Focused Ultrasound?

Early stage, noninvasive, therapeutic technology

Alternative or complement to surgery, radiation therapy, drug delivery

*Potential* to transform treatment

Improved outcomes, decreased cost
Essential Tremor

Awake, no anestheisia
No incisions
No burr holes
No electrodes
No infection
No blood clots
No brain damage
The Principle

Multiple intersecting beams of ultrasound

- Focused accurately (submillimeter)
- Target in body
- Individual beams pass harmlessly through adjacent tissue
- Profound effect at point of convergence
Adjacent tissue sparing

Liver

Brain
Effects at the focal point

Platform technology
18+ Biomechanisms

Variety of effects, variety of disorders
Biomechanisms

- Thermal ablation
- Histotripsy
- Focal drug delivery
- Blood-brain barrier opening
- Immunomodulation
- Neuromodulation
- Radiation sensitization
- Drug activity enhancement

- Amplification of cancer biomarkers
- Dissolve clots: sonothrombolysis
- Coagulate blood vessels
- Vasodilation
- Vasoconstriction
- Stem cell delivery
- Sonodynamic therapy
Neuropathic Pain

- University of Maryland
- Focused ultrasound target: thalamus
- Active recruitment of patients

Researchers at University of Maryland School of Medicine are testing ultrasound to treat neuropathic pain
Back Pain – Facet Arthritis

- McGill University, Montreal, Canada
- Focused ultrasound target: nerves surrounding and innervating the painful facet joint
- Recruitment complete, awaiting results
Knee Pain – Osteoarthritis

- Knee pain secondary to osteoarthritis
- Kochi University Hospital, Kochi, Japan
- Focused ultrasound target: nerves along the inner, lower knee joint surface
- Recruitment complete, awaiting results
Craniofacial Neuropathic Pain

- University of Virginia
- Focused ultrasound target: thalamus
- Active recruitment of patients
Stump Neuromas

- Painful amputation stump neuromas
- Rambam Medical Center, Haifa, Israel
- Focused ultrasound target: stump neuroma
- Actively recruiting patients
Global Development Landscape – More than 215,000 Total Treatments

215,720 Total Treatments

- Uterine fibroids: 89,353 (41%)
- Prostate diseases: 69,825 (32%)
- Breast tumors: 21,444 (10%)
- Liver tumors: 18,000 (8%)
- Glaucoma: 6,142 (3%)
- Brain: 1,221 (1%)
- Other: 9,735 (5%)

- Other: 9,735
- Brain: 1,221

9,735 Total Other Treatments
1,221 Total Brain Treatments
Global Development Landscape

- Essential Tremor: 833 (68%)
- Parkinson's disease: 187 (15%)
- Neuropathic pain: 97 (8%)
- Brain tumors: 27 (2%)
- Mental health*: 21 (2%)
- Alzheimer's disease: 11 (1%)
- Other movement disorders**: 8 (1%)
- Other brain: 37 (3%)

* Includes OCD and Depression
** Includes Epilepsy and Dystonia

Total Other Treatments:
- Bone metastases: 2,173 (22%)
- Thyroid nodules: 803 (8%)
- Pancreatic cancer: 705 (7%)
- Hypertension: 69 (1%)
- Back pain: 60 (1%)
- Parathyroid: 55 (1%)
- Cancer unspecified*: 5,590 (57%)
- Other: 280 (3%)

* Not all manufacturers are providing specific cancer indications. The Foundation is working to clarify this for 2019 State of the Field Report.
Process is complicated and inefficient

- Evidence, safety, efficacy, cost
- Design, engineering, manufacturing
- Training and credentialing
- Insurance reimbursement
- Physician advocacy
- Idea generation
- Regulatory approval
- Patient advocacy
- Marketing, sales, support
- Technology R&D
- Physician and patient awareness/education
- IP generation and protection
- Pre-clinical proof of concept
- Economic value proposition
- Design, engineering, manufacturing
Complex ecosystem

- Private philanthropy
- Academic research sites
- Disease specific foundations
- Venture capital, private equity
- Industry
- Payers; public and private
- Patient advocacy organizations
- Treatment facilities
- Physicians, numerous specialties
- Medical societies
- Media
- Patient

Disease specific foundations
Impediments

- Awareness: patients and physicians
- Robust evidence; safety, efficacy, cost
- Regulatory approvals
- Insurance reimbursement
- Inertia: physicians resistance to change
- Turf battles: medical specialists, manufacturers
- Cultural Issues: patient centricity, urgency, collaboration
- Purchasing value proposition
The solution: overcome impediments

Obscure: No model, example or formulas
Obligated to invent
Focused Ultrasound Foundation

Unique medical research, education, advocacy organization

- Founded 2006, Charlottesville, Va: Global impact
- Tax exempt
- Entrepreneurial, high impact, market driven, action and results oriented

Catalyst to accelerate the development and adoption of FUS
Influence direction

Identify critical unmet clinical needs

Set research priorities

- Biomechanisms
- Clinical indications

Change culture

- Patient centric
- Urgency
- Collaboration
Create Evidence: Research

Organize, conduct and fund research
- Clinical, preclinical, technical
- Focus: Brain, cancer immunotherapy
- Largest non-governmental funding source

Convene the Community

Organize meetings, symposia, workshops
- Exchange knowledge and ideas
- Foster collaborations and partnerships
- Stimulate innovation

Workshops

Symposia

$4.8M

$27.5M
Positioning

- Private philanthropy
- Academic research sites
- Disease specific foundations
- Media
- Venture capital, private equity
- Payers; public and private
- Patient advocacy organizations
- Treatment facilities
- Physicians, numerous specialties
- FDA
- Patient
- Industry

-focused ultrasound foundation
Adoption
Adoption: without Foundation
Investment Activities Impact
Saving Time = Saving Lives
Exoskeletal Assisted Walking & Rehabilitation of Spinal Cord Injury

Ashraf S. Gorgey, MPT, PhD FACSM, FACRM
Director of Spinal Cord Injury Research
Hunter Holmes McGuire VAMC
Associate Professor, Phys. Med& Rehab
Virginia Commonwealth Univ.
The SCI Exercise and Body Composition Laboratory

Sarcopenic Obesity

Cardio-Metabolic Comorbidities

???
Prevalence of Obesity after SCI

Obesity Trends* Among U.S. Adults & SCI Adults

> 30% for SCI
20-29% for Adults

Behavioral Risk Factor Surveillance System, CDC

Obesity Trends among SCI Adults

2011-2013

Obesity Trends* Among U.S. Adults
Body Composition Assessment
Exoskeleton Program at McGuire VA Hospital
Standing Upright Improves Quality of Life to Our Veterans
Why Different Brands of Exoskeletons?

- ReWalk exoskeleton
- Ekso GT® exoskeleton
- Indego® exoskeleton
- REX® exoskeleton
## Different Brands of Exoskeletons

<table>
<thead>
<tr>
<th>ReWalk</th>
<th>Ekso GT</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ First powered exoskeleton approved by FDA for home use</td>
<td>➢ Grip is less critical</td>
</tr>
<tr>
<td>➢ strong grip is required for crutch use</td>
<td>➢ Can be used with crutches or a walker</td>
</tr>
<tr>
<td>➢ A communicator watch is worn by the user to switch between modes (sit, stand and walk)</td>
<td>➢ Not authorized for community use</td>
</tr>
<tr>
<td>- “By-Pass” mode to activate the device directly</td>
<td>➢ fastest swing time: 0.8 second</td>
</tr>
<tr>
<td>- The “stair” mode is currently locked for devices sold in the U.S</td>
<td>➢ Gait training mode:</td>
</tr>
<tr>
<td>➢ Device’s parameters (i.e. AMPS, tilt angle, step time, delay between steps) are modified through the ReWalk interface (authorized users only)</td>
<td>- First step- manually controlled by the therapist</td>
</tr>
<tr>
<td>- Step time (1.2-0.6 seconds)</td>
<td>- Pro step mode- offers complete assistance</td>
</tr>
<tr>
<td>- Delay between step (0-350 ms)</td>
<td>- Pro step plus mode- adaptive assist, mainly intended for incomplete SCI</td>
</tr>
<tr>
<td>- Progression is made based on user proficiency</td>
<td>➢ FDA approved for clinical, but not yet home use</td>
</tr>
</tbody>
</table>
Different Brands of Exoskeletons

**Indego**
- Can be used with crutches or Walker
- The lightest FDA approved EAW device
  - 12 kg (26 lbs) including battery
- Can be worn while sitting in a rigid frame
  - five modular segments that can be assembled on user
- Modes are activated through a phone app
- FDA approved for home use

**REX**
- Heaviest EAW device
  - 110 kg
- Authorized for supervised use in hospital and rehabilitation centers
- Self supporting
  - Offers greater stability than most exoskeleton
  - World's first "hands free" device
- **REXercise**
  - Performs static and dynamic lower body exercises such as lunges and squats
Exo-Assisted Rehab. after SCI
Features Specific to different Brands

<table>
<thead>
<tr>
<th>Feature</th>
<th>ReWalk</th>
<th>Ekso</th>
<th>Indego</th>
<th>REX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country of Manufacture</td>
<td>Israel</td>
<td>United States</td>
<td>United States</td>
<td>New Zealand</td>
</tr>
<tr>
<td>U.S. Food and Drug Administration class II designation</td>
<td>Medical center and home</td>
<td>Medical center only</td>
<td>Medical center and home</td>
<td>Not approved in United States</td>
</tr>
<tr>
<td>Cost in U.S. dollars</td>
<td>$67,000</td>
<td>$130,000</td>
<td>$73,000</td>
<td>$160,000</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight of the unit (lbs.)</td>
<td>66</td>
<td>50</td>
<td>27</td>
<td>110</td>
</tr>
<tr>
<td>Maximum weight capacity (lbs.)</td>
<td>220</td>
<td>220</td>
<td>220</td>
<td>220</td>
</tr>
<tr>
<td>Maximum user height (inches)</td>
<td>76</td>
<td>76</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>Controller</td>
<td>Arm watch</td>
<td>Hand-held controller</td>
<td>iPod and posture combination</td>
<td>Joystick</td>
</tr>
<tr>
<td>Wheelchair accommodation</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Stair climbing function</td>
<td>Yes (disabled)</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Functional electrical stimulation unit</td>
<td>No</td>
<td>No</td>
<td>Yes (prototype)</td>
<td>No</td>
</tr>
</tbody>
</table>
**Summary of Major Clinical Trials**

<table>
<thead>
<tr>
<th>TABLE 44.2 Summary of Clinical Trials of Exoskeletons in Spinal Cord Injury</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ReWalk</strong></td>
</tr>
<tr>
<td>Publications</td>
</tr>
<tr>
<td>Approved level of spinal cord injury</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Mechanics of walking</td>
</tr>
<tr>
<td>Maximum number of sessions reported</td>
</tr>
<tr>
<td>Maximum duration of use reported (min)</td>
</tr>
<tr>
<td>Frequency of training</td>
</tr>
<tr>
<td>Maximum speed (m/s)</td>
</tr>
<tr>
<td>Mean gait speed (m/s)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
</tr>
<tr>
<td>Metabolic equivalents</td>
</tr>
<tr>
<td>Rate of perceived exertion</td>
</tr>
<tr>
<td>Oxygen uptake (VO₂) (mL/kg/min)</td>
</tr>
<tr>
<td>Spasticity control</td>
</tr>
<tr>
<td>Variable assist</td>
</tr>
<tr>
<td>Gait pattern</td>
</tr>
<tr>
<td>Walker</td>
</tr>
<tr>
<td>Crutches</td>
</tr>
</tbody>
</table>
Expectations, Reality & Limitations

➢ Gait speed
➢ Weight, width, reliability and durability
➢ Level of injury
➢ Pressure injuries
➢ Stair functions
➢ Balance and caregivers
➢ Ability to combine with wheelchair

➢ Wheelchair remain primary mobility tool.

➢ Benson el al. (2016) reported low satisfaction in participants expectation

➢ Zelig et al. (2012) reported high satisfaction scores in the following measures: training session, safety and pain or fatigue.

➢ All participants were motivated to continue EAW
Background/Purpose

➢ The American Heart Association (AHA) and the American College of Sports Medicine (ACSM) have agreed that 30 minutes of daily exercise may mitigate several of the health-related consequences resulting from a sedentary lifestyle.

➢ Most recently exoskeletal assisted walking units became available as a rehabilitation tool to facilitate locomotion in persons with SCI.
DXA-Total and Regional Bone Scans
Main Outcome Measures

- Main outcome measurements over 10-15 weeks were
  - walking time
  - stand-up time
  - ratio of walking to stand-up time
  - number of steps

- The energy expenditure (EE) and body composition were also measured.
A C5/C6 Complete SCI
Exoskeleton training for 10-15 weeks

Weeks of Training

Walk Time (minutes)

Steps

Subj. A
Subj. B
Subj. C
Subj. D

0 2 4 6 8 10 12 14 16

0 500 1000 1500 2000 2500

0 1000 1500 2000 2500

0 2 4 6 8 10 12 14 16
Energy Expenditure during Exoskeleton training
# Body Composition-DXA

<table>
<thead>
<tr>
<th></th>
<th>Arms</th>
<th>Legs</th>
<th>Trunk</th>
<th>Android</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%Fat Pre-training</strong></td>
<td>31.5</td>
<td>44</td>
<td>45.5</td>
<td>44.7</td>
<td>42.1</td>
</tr>
<tr>
<td><strong>%Fat Post-training</strong></td>
<td>35</td>
<td>46</td>
<td>45.4</td>
<td>44.8</td>
<td>42.7</td>
</tr>
<tr>
<td><strong>Fat Pre-training (kg)</strong></td>
<td>3.9</td>
<td>10.5</td>
<td>24.4</td>
<td>4.12</td>
<td>40</td>
</tr>
<tr>
<td><strong>Fat Post-training (kg)</strong></td>
<td>4.3</td>
<td>9.6</td>
<td>23</td>
<td>3.8</td>
<td>38.2</td>
</tr>
<tr>
<td><strong>Lean mass Pre-training (kg)</strong></td>
<td>8.4</td>
<td>13.3</td>
<td>29.3</td>
<td>5.1</td>
<td>55</td>
</tr>
<tr>
<td><strong>Lean mass Post-training (kg)</strong></td>
<td>8.2</td>
<td>11.5</td>
<td>27.5</td>
<td>4.7</td>
<td>51.3</td>
</tr>
<tr>
<td><strong>BMC Pre-training (kg)</strong></td>
<td>0.61</td>
<td>1.43</td>
<td>2.14</td>
<td>0.16</td>
<td>4.8</td>
</tr>
<tr>
<td><strong>BMC-Post-training (kg)</strong></td>
<td>0.60</td>
<td>1.4</td>
<td>2.02</td>
<td>0.14</td>
<td>4.7</td>
</tr>
<tr>
<td><strong>Total mass-pre training</strong></td>
<td>13</td>
<td>25</td>
<td>55.8</td>
<td>9.4</td>
<td>100</td>
</tr>
<tr>
<td><strong>Total mass-post training</strong></td>
<td>13.1</td>
<td>22.5</td>
<td>52.6</td>
<td>8.6</td>
<td>94</td>
</tr>
</tbody>
</table>
A C5/C6 Complete SCI-28 weeks of training
Standup time & walk time

Standup Time (minutes) vs. Weeks of Training

Walk Time (minutes) vs. Weeks of Training
Ratio of walk time to standup time & number of steps
Feasibility of robotic exoskeleton ambulation in a C4 person with incomplete spinal cord injury: a case report

Robert M. Lester¹ - Ashraf S. Gorgey¹,²

Received: 4 December 2017 / Revised: 29 January 2018 / Accepted: 30 January 2018
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Figure 1

a.  
b.  
c.
Near-infra-red spectroscopy (NIRS)
Potential Benefits of Exoskeletal training

Improvement in body composition
- A pilot study from James J. Peters VAMC in Bronx, NY showed decreased in fat mass and total body mass after 36 sessions of EAW (n=9) using the ReWalk (Spungen et al. 2013)
- A single case report shows a loss of 2 kg of fat mass and 4 kg of lean mass after 15 weeks of training using Ekso (Gorgey et al. 2017)
- More studies are needed to predict the effect of EAW on body composition

Spasticity
- Reported decrease in spasticity after EAW training (Benson et al. 2016, Kressler et al. 2014)

Bowel Function
- Improved bowel activity was reported several studies (Benson et al. 2016, Miller et al. 2016)
- Evidence are not conclusive.
- On going multi-center study included bowel function as an important outcome measure

Quality of life
- Evidence indicate positive affects on activity participation, pain and fatigue (Zeilig et al. 2012)
- Additional improvement in pain, fatigue posture and sleep issues were observed (Kozlowski et al. 2015, Kressler et al. 2014)
- May reduce the number of therapists needed for rehabilitation and increase independence after SCI
EXTra-SCI

ClinicalTrials.gov

Trial record 1 of 18 for: Spinal Cord Injuries | Richmond, Virginia, U.S.

Exoskeleton and Spinal Cord Injury (EXTra-SCI)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

Sponsor:
McGuire Research Institute

Information provided by (Responsible Party):
Ashraf Gorgey, McGuire Research Institute

ClinicalTrials.gov Identifier: NCT03410550

Recruitment Status: Recruiting
First Posted: January 25, 2018
Last Update Posted: July 26, 2018

See Contacts and Locations
Epidural Stimulation in Rehabilitation after SCI
Body Weight-Supported Treadmill Training (BWSTT)

- Harness strapped around body supports a pre-determined percentage of pt’s weight

- Facilitates walking-related sensory input for a reciprocal gait pattern through hand placement
Progression of SCS-enabled stepping performance on a treadmill (Gill et al. 2018)
Single vs. Interleaved SCES (Gill et al. 2018)
# Epidural Stimulation with Exoskeletal Training

<table>
<thead>
<tr>
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<tr>
<td>4</td>
<td>15</td>
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</table>

- **Frequency**: 40Hz
- **Voltage**: 6V - 7V
- **Duration**: 420 µs
Epidural Stimulation with Exoskeletal Training
Future Directions & Recommendations

➢ Malleable frames
  ➢ More flexible range of motion
  ➢ Currently are made of rigid frames that are likely to exert external inertia to allow sagittal movements

➢ Pneumatic muscles or flexible actuators
  ➢ produce active plantar flexion torque
  ➢ currently movement at the ankle is determined by a fixed or spring activated AFO

➢ Combing FES with EAW
  ➢ FES stimulate muscle contractions
  ➢ potential to strengthen in addition to locomotion

➢ Brain Machine interfaces to control exoskeletons
  ➢ electroencephalographic signals to decode gait intentions
Summary/ Conclusions

- Evidence support EAW may improve quality of life, level physical activity & independence in people with SCI.
- Currently only two brands have FDA clearance for home use (ReWalk and Indego).
- Eligible user should be educated about the device and understand the existing limitations.
- EAW is a skill and the learning curve varies across individuals. It can be used as an effective platform to combine with different...
Acknowledgements
Funding Sources

- Department of Veterans Affairs
- Department of Defense-CDRMP
- National Science Foundation