Challenges in Neuromodulation Therapy

Milton M. Morris, PhD, MBA

Principal
MEH BioMedical, LLC

February 25, 2015
Neuromodulation offers multiple indication therapy

**FDA APPROVED**
- Deep Brain Stim: Parkinson’s Disease, Dystonia, Essential Tremor, Obsessive Compulsive Disorder
- Vagus Nerve Stimulation: Depression, Epilepsy
- Spinal Cord: Pain
- Sacral Nerve Stim: Urinary Incontinence, Fecal Incontinence
- Percutaneous Tibial Nerve Stim: Urinary Incontinence
- Cortical Stim: Epilepsy
- Peripheral Nerve Stim: Migraines, Extremity Pain
- Carotid Artery, Sinus Stim: Hypertension
- Hypoglossal & Phrenic Nerve Stim: Sleep Apnea
- Spinal Cord Stim: Angina
- Gastric Stim: Obesity
- Sacral & Pudendal Nerve Stim: Interstitial Cystitis, Sexual Function, Pelvic Pain
- Percutaneous Tibial Nerve Stim: Urinary Incontinence

**EMERGING**
- Deep Brain Stim: Obesity, Stroke Recovery, Depression
- Deep Brain Stim: Epilepsy
- Peripheral Nerve Stim: Migraines, Extremity Pain
- Carotid Artery, Sinus Stim: Hypertension
- Hypoglossal & Phrenic Nerve Stim: Sleep Apnea
- Spinal Cord Stim: Angina
- Gastric Stim: Obesity
- Sacral Nerve Stim: Urinary Incontinence, Fecal Incontinence
- Sacral Nerve Stim: Sexual Function, Pelvic Pain
- Percutaneous Tibial Nerve Stim: Urinary Incontinence

**FUTURE**
- Deep Brain Stim: Alzheimer’s, Anxiety, Bulimia, Tinnitus, Traumatic Brain Injury, Tourette’s, Sleep Disorders, Autism, Bipolar
- Vagus Nerve Stim: Alzheimer’s, Anxiety, Obesity, Bulimia, Tinnitus, Obsessive Compulsive Disorder, Heart Failure
- Spinal Cord Stim: Asthma
- Gastric Stim: Bulimia, Interstitial Cystitis
Epilepsy by the numbers

**Epilepsy**

4th most common neurological disease after migraine, stroke and Alzheimer's disease

9 MILLION

People living with epilepsy in United States, Europe, and Japan

<3% chance of seizure freedom after 2 AED failures

400,000

People indicated for VNS Therapy® in US

Direct and indirect costs of $13.5B per year in US alone

25-40X

Mortality rate vs. general population

Source: CDC, WHO, IOC report on Epilepsy

**Status of Neuromodulation Therapy(ies)**

- FDA: Approved
- CMS: Favorable Coverage Recommendation
Depression by the numbers

**Depression**
Major depressive disorder (MDD) is the second leading cause of disability worldwide*.

**18 MILLION**
People affected at any one time in United States

**350 Million**
People worldwide affected by depressive illness

**4 Million**
Approx. 25% of depressed individuals (U.S.) are treatment resistant

Direct and indirect costs of > $43B related to lost productivity in the workplace per year

>39,000
Suicide deaths per year in the U.S.

**Status of Neuromodulation Therapy(ies)**
- FDA: Approved (VNS)
- CMS: Non-Favorable Coverage Recommendation

Source: CDC, WHO, NAMI
*(Ferrari et al, 2013)*
Heart Failure by the numbers

- **Heart Failure**
  - is a serious and progressive condition; incidence increases dramatically with age

- **10-12 Million**
  - people living with heart failure in the US and Europe

- **5-Year Mortality**
  - for 50% of patients

- **700,000**
  - newly diagnosed cases annually

- **Direct and indirect costs of $40B**
  - per year in US alone

- **Most Common Reason**
  - for hospitalization in Medicare patients

Status of Neuromodulation Therapy(ies)
- FDA: Human Clinical Trials (Pivotal & Pilots)
- CMS: NA
Industry Challenges in the Neuromodulation Field

Limitations in Funding Driven by Inconsistent Performance/Results:

- Recent history of study failures has limited investment and innovation
  - CVRx, NorthStar, Apnex, Transneuronix, Cyberonics (depression), Boston Scientific (heart failure), many others
  - What are key learning's to improve success, or to fail fast?

- Lengthy clinical studies and long regulatory processes
  - Can dampen enthusiasm for investment and innovation

- Reimbursement challenges
  - FDA approval does not guarantee national reimbursement coverage
Industry Challenges in the Neuromodulation Field

Limitations of Clinical Past/Current Clinical Studies:

• Implantable neuromodulation therapies are typically indicated for drug refractory, treatment-resistant patients
  – Difficult to treat patient population (different etiologies, phenotypes, patient’s physiology and co-morbidities, etc.)

• Difficult to do a blinded study, control group can perceive low levels of stimulation

• The clinical effect is not always obvious and treatment effect may take extended time (months)

• For many therapeutic approaches, no quantitative endpoints are known/available, only qualitative end points

• Animal models may not translate well to human
Industry Challenges in the Neuromodulation Field

Limitations in Known Technology, Science, & Physiology:

• Technical limitations such as **imprecise targeting**
  – Which cortical pathways & are they stimulation dependent?
  – How to best modulate neuronal activity (**inhibit/excite**)?
  – Methods to identify optimal stimulation parameters.

• Clinical therapeutic response may not be immediate or obvious
  – e.g., Depression (1 to 6 months), Parkinson’s (immediate)

• Limited sensing capability
  – Biomarkers of response are not readily identifiable in today’s approved treatments.

• **Response Prediction**: Identify patients that will respond to therapy prior to implantation.

• Incomplete knowledge of mechanisms of therapeutic action
Human Cervical Vagus Nerve

The human vagus nerve
• ~ 100,000 axons
• 80% afferent, 20% efferent
• 80% are C-fibers, 20% are A, B fibers

• Which fibers are responsible for therapeutic effect?

• Where do these fibers project into the CNS and peripherally?

• What neuromodulatory systems are excited/inhibited?

Nemeroff CB. *Neuropsychopharmacology.* 2006;31:1345-55.
Bilateral projections on nucleus tractus solitarius (NTS)
Locus coeruleus supplies norepinephrine
Raphe magnus nuclei supply serotonin
Parabrachial nucleus of pons has widespread cerebral projections

Nerve Fiber Stimulus Activation

Vagus nerve cross section, dispersed fiber (axon) types

- Electric fields modeled using finite element (ANSYS)
- Comparison of fiber activation in chronic vs. acute implant
- % fiber activation function of: charge/density, dist. from electrode, acute vs chronic condition
- Challenge: How can we best activate the right fiber groups but minimize adverse events?
  - Incorporate nerve action potential sensing?

Helmers et al. 2012
Summary Challenges (& Opportunities) for advancing the field of neuromodulation

Challenges: Understanding the “neural code”
- What are the mechanisms of action that lead to positive reproducible outcomes?
- How can stimulation parameters be optimized for specific patients?
- How can we make relevant biomarkers available in real-time?
  - Closed-Loop stimulation
- Can plasticity effects of neuromodulation be predicted?
  - Improved clinical trial Designs

Opportunities: Novel Technologies and Tools
- Advanced brain imaging technologies
- Optogenetics
- Big Data
- Nanotechnologies
- Signal processing methods, Adaptive algorithms
Challenges in Neuromodulation Therapy

Thank You

Milton M. Morris, PhD, MBA
Principal
MEH BioMedical, LLC

February 25, 2015