Addressing Neurological Disorders with Neuromodulation

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This lecture will include a discussion of FDA Approved and Off-label indications

Disclosures:
• DBS for Depression and OCD Clinical trial funding, Medtronic
• Educational Consulting-Medtronic Neurological
• Intellectual property and potential equity position, IntElect Medical and Autonomic Technologies
• Ownership Equity, Surgivision and Autonomic Technologies
Neurological Diseases

- Neurological disorders affect 100 million in the US
- Increasingly common in the aging population
  - Approximately 20% of US population is over age 60
- Can cause progressive loss of function and chronic disability
  - Patient, family, caretakers
  - Enormous burden, societal health care spending, disability care, job limitations, dependence of others
- Neurological Disorders Consume Over One Third of the Global Chronic Disease Health Burden
- EU study concluded that the cost of neurological disorders is more than cancer and heart disease combined
Despite advances in medication and other treatment approaches:
• 10-20% of patients become intractable over time with impaired function, compromised quality of life and suffering

Neuromodulation can potentially help these patients
Neuromodulation Approaches
Stimulators
Infusion Device
Lesioning
Gene therapy
Non-surgical
Brain Stimulation
“It is the writer’s conviction that focal controlled stimulation of the human brain is a new technique… that is here to stay, having potential advantages over… destructive procedures by virtue of the fact that it does not destroy brain tissue but nevertheless seems capable of yielding satisfactory therapeutic results.”

• J.L. Pool (Columbia University)-1948

Used silver electrodes into the Caudate nucleus and connected it to an implanted induction coil
Severe depression secondary to advanced Parkinson’s disease
Brain Stimulation

- The first report of direct stimulation of the human brain.

Roberts Bartholow
(Cincinnati, Ohio)
1874
DBS for Pain

• DBS for Pain
  • Early Development of DBS technology (1970’s)
  • Hosobuchi et al. (1973)
    • Thalamic DBS for neuropathic facial pain
  • Richardson and Akil (1977)
    • PAG/PVG/CM/Pf for chronic pain
Deep Brain Stimulation for Movement Disorders

- Bechterva-Russia
  - 1970’s
- Benabid-France
  - 1987- Vim Stimulation for ET
  - 1993-STN stimulation for PD
- Siegfried-Switzerland-GPI 1987
Deep Brain Stimulation (DBS): 2010

• DBS Therapy is approved for the treatment of
  • Essential Tremor
    • FDA approved in 1997
  • Parkinson’s disease
    • FDA approved in 2002
  • Dystonia
    • FDA approved (HDE) in 2003
  • Obsessive Compulsive Disorder
    • FDA approved (HDE) in 2009
DBS: Implantable Components

- Lead
- Extension
- Neurostimulator (implantable pulse generator)
- Clinician programmer
- Patient controller
- Frequency, intensity, pulsewidth, combination of contacts
Deep Brain Stimulation (DBS) for Parkinson's Disease

DBS Improves
Tremor
Rigidity
Slowness of movement
Reduces medication intake
Reduces dyskinesias
DBS : 2010

• > 23 years of safety
• > 65,000 DBS Implants worldwide
• >2500 published articles on DBS
• Prospective and randomized controlled studies
  • Improvements demonstrated in
    • Standardized Scale/measures of disease
    • Quality of life measures, Co-morbid conditions
    • Medication intake, Chronic care costs
DBS for Obsessive Compulsive Disorder (OCD)

60% of Patients with severe end stage OCD were responders with DBS

Improvement in OCD scores (YBOCS), Quality of life (GAF)
And depression (HAM-D)--------Led to new indication for depression

FDA approval US-HDE 2009
DBS for Depression

• Open label Phase I/II study is promising
  • 60% of patients with severe depression were responders
    • 1/3 in remission

• Phase III randomized, Controlled Trial underway-2009
  • Medtronic Sponsored Study
    • VC/VS target
  • St. Jude sponsored study
    • Area 25-subgenual cingulate cortex
DBS for Epilepsy

Prospective randomized studies
- Medtronic -SANTE- Phase III
  - Anterior thalamus
  - >50% responders
    - FDA review panel
    - FDA approval under review
- Neuropace-Phase III
  - Outcome met responder criteria
DBS:2010

- FDA Approved indications
  - Parkinson’s, Essential tremor, dystonia
  - OCD
- Phase III completed, FDA review
  - Epilepsy-Anterior nucleus
  - Epilepsy-Responsive stimulation
- Phase III-In process-2209
  - Depression-VC/VS
  - Depression-Cg 25
- Early stage clinical trials
  - Anxiety disorders
  - Addictions
  - Tourette’s
  - Chronic pain and headaches
  - Tinnitus
  - Traumatic brain injury
  - Obesity
  - Anorexia
  - Alzheimer’s
  - PTSD
DBS

• Rapidly Growing field
  • Multiple disciplines and multiple practitioners
• Multiple current and Emerging indications
• Increasing acceptance in medical and lay community
• Growing area of research opportunities
DBS

- Has helped thousands of patients
- Enormous Potential
- Has DBS come of age?
Grand Challenges in DBS
DBS: Study Design

• Proof of Concept can be Challenging
  • Animal models are difficult and not always predictive of the human condition
  • Initial observations and optimism from human case studies need to carefully evaluated for next steps
DBS: State of Evidence

• Large body of literature, most are non controlled studies

• Movement Disorders
  • Parkinson’s Disease
    • Few class I and II, mostly Class III
  • Essential Tremor
    • Class III open label studies
  • Dystonia
    • Few class I, mostly Class III

• Epilepsy
  • Randomized, controlled, blinded study-Anterior thalamus target-Medtronic
  • Randomized, controlled, blinded study-Neuropace

• OCD
  • Open label study-VC/VS target- Medtronic
  • Randomized controlled, blinded study in progress-NIMH Grant

• Depression
  • Open label phase I/II- VC/VS, Cg25 target
  • Current randomized, controlled, blinded study in progress-Medtronic, St. Jude

• All other indications
  • Class III-retrospective open label, case reports

• Stroke
  • Randomized, controlled, blinded study failed to show significance
    • Company no longer in existence
DBS: Clinical Trial Design Considerations

- Open label studies-pilot trials
  - Safety and initial efficacy observations
  - But-Retrospective studies have limited impact

- Blinded, randomized, controlled, sham stimulation are necessary

- Variables to consider
  - Human Variables
    - Patients Selection criteria
    - Disease heterogeneity
    - Placebo considerations
  - Intractable/refractory status
    - Suffering patients
  - Comparison to placebo, best medication and other therapies
  - Follow-up assessment standardization
    - Primary outcomes
    - Secondary outcomes, Quality of life measures
    - Cost of living, medication use
  - FDA and Regulatory input and guidance
  - Ethical considerations
**DBS Surgery: Who are the Candidate?**

- **Advanced disease**
  - last stages of the disease?
    - Neurostimulation may be less effective as the disease progresses
  - DBS implant age 7-91
- **Optimization of medications**
  - How many medications? How many years
- **Consideration of co-morbid conditions**
- **Neuropsychological evaluation**
  - Psychological screening
- **Multidisciplinary evaluation and partnership is crucial**
DBS Targets
Scientific Rationale

- DBS Target Selection
  - Anatomic, pathologic, physiologic, animal, clinical, imaging studies
  - Improved understanding of dynamic and plastic networks or brain circuitry in normal and disease conditions
    - Motor, sensory, cognitive, behavioral systems
  - Networks can be modulated electrically, chemically and via other mechanisms
  - Modulation can occur at multiple locations/nodes in the network/circuitry
    - Brain-Cortical, sub-cortical
    - Spinal cord
    - Peripheral nerves
Behavior, Emotional and and Cognitive Neural Circuits

- Mood
  - Depression, apathy
- Anxiety
  - Obsessions, compulsions, fear
- Behavioral self awareness and self regulation
- Decision making
- Reward and motivation
- Cognition
- Memory
- Integration with sensory and motor systems
Mechanisms
DBS Mechanisms

- Depends on the location and structures influenced
  - Axons, neurons
  - Upstream, downstream
  - Network modulation (cortical/sub-cortical)
- Parameter dependent
  - Frequency, pulsewidth, contacts, intensity
  - Waveform
- Inhibition-information blockade
- Activation
- Modulation
- Regulation and normalization of abnormal network activity
DBS: Mechanisms

- Acute and chronic effects
- Cellular
  - Gene and protein expression changes
  - Receptor density changes
- Network effects
  - Facilitation of connections
- Plasticity
- Brain imaging studies
  - PET, fMRI, MEG, others…
- Using imaging as a marker
  - Responder vs. non responder
Sample axial images showing BOLD activation effects of DBS for each of the four contacts examined in a patient with OCD. The idealized position of the DBS leads is provided for illustrative purposes only. [Cd = Caudate]

PARAMETERS

130 pps
210-us PW
8.0-Volts
The DBS Implant System
The DBS Electrode

• Electrodes
  • Currently cylindrical- 4 contacts
  • Emerging devices
    • Multiple contacts, 8-16-32
    • Directional stimulation
    • Multiple arrays
  • Sensors
    • Chemical and electrical input and output
  • Is the same cylindrical electrode appropriate to be placed in various targets in the brain

• Other system components
  • Antibiotic coating, MR compatibility
  • System durability-Lead fracture, fraying
The Pulse Generator

- Miniaturization
- Powering mechanisms
  - Rechargeable systems
  - Battery improvements
  - Harnessing body’s mechanical energy
- Circuitry improvements
  - Data storage
  - Power generation
  - Feedback, sensing capability
- Programming Parameter
  - Frequency, PW, Pairing, shaping of field
  - Waveform advances
- Other stimulators
  - Optical

- MR compatibility
  - Chokes, uncoupling
The DBS system can be influenced by close proximity to:

- Power generators
- Metal detectors
- Security Devices
- Power lines
- Gas or Electric Motors
- Transmitting towers
- Magnets
- Arc Welding
DBS and MRI

MRI is necessary for evaluation of patient
DBS has MRI Conditional Safety status

Problems with DBS and MRI
Magnetic field interactions
Heating
Induced currents
Operational/functional disruption
Modeling

- Computerized models
  - MRI safety
  - Electrical field visualization
    - Programming
  - Surgical planning
Technology considerations

• Current Devices are clinically effective
• But, need to evolve-The Pace of development is slow
  • Laboratory findings need to be translated into the clinical arena
  • Industry participation
    • Limited R&D
• Collaboration
  • Engineering
  • Neuroscience
  • Clinicians
  • Imaging
  • Computer science
DBS Surgical Procedure
DBS: Risks and Complications

• Surgery related
  • Hemorrhage, stroke
  • Infection
  • Erosion
  • Hardware related

• Stimulation related
  • Usually can be minimized or eliminated by adjusting stimulation settings
  • Reversible paresthesia, dysarthria, muscle contraction
The Surgical Implant Procedure

- Safety
- Minimally invasive
- Brief inpatient procedure
- Precise implantation into the exact location
- Reproducible implantation
- Low side effect profile
- Long-term durability
DBS Surgery: 2010
Targeting and Planning

• Anatomical Targeting
• Image guidance systems
• Stereotactic headframe
• Frameless
Physiological Mapping

- Microelectrode recording (MER)
- Microstimulation
- Macrostimulation with DBS electrode
Challenges

• DBS is helping tens of thousands of patients now and potentially hundreds of thousands in the future

• Dramatic benefits, but mechanisms are not well understood

• The science is lagging behind the therapy
  • Need more research

• Need to increase the pace of development

• Collaboration between engineers and clinicians is necessary
Neuromodulation:

- An increasingly utilized therapeutic option
- Implantable devices changing the way chronic diseases are treated
- Provides Hope
- Improves quality of life
  - Self care, independence, social and occupational functioning
- Decreases burden of chronic care costs
- Enormous POTENTIAL