Cyberonics and Vagus Nerve Stimulation

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Agenda

- Pacemaker Engineering – 1970’s
- The Cyberonics Story
- Vagus Parasympathetic System Brain Mapping
- Potential new therapies
- Potential new technologies
- Conclusion
July 19, 1969
* 1969 – Demand Pacemakers (VVI)
* Devices large (59 mm x 68 mm x 24 mm), heavy (135 – 150 gm), epoxy encapsulated, mercury zinc batteries which outgassed H2O and H2
* Unknown Problems
  * Short battery life (18 months)
  * Discrete transistors, carbon resistors, reliability problems
  * EMI issues unknown
* Production Challenges – Each device custom ordered
Cordis Pacemaker

136 grams, 24 mm thick
* Cordis integrated circuit programmable pacer (1972)
  * Potential to become market leader
  * Unknown reliability issues – epoxy out gassing, thick film material change
* CPI - Lithium Battery 1975
  * Hermetic sealed can for electronics and battery
    * Solved component reliability problems
    * Solved battery life problems
    * Solved EMI problems with feed thru capacitors
* FDA Medical Device Act 1976
Epilepsy: A Window to Brain Mechanisms *Lockard 1980*

Cybernetics: The comparative study of automatic control systems of the brain and nervous system *Webster’s Dictionary*

Improved Understanding of the vagal brain projections and the vagus parasympathetic system from the vagus nerve stimulation (VNS) treatment of epilepsy.
Cyberonics Background

1986

- Epilepsy affected over 2 million patients and over 30% were refractory to medications
- Only a few drugs were approved to treat epilepsy
- New treatment options were urgently needed
- 1986 AES meeting: Vagus stimulation was a radical idea; only Dr. Kiffin Penry saw the potential
Early Successes

- Dr. Penry’s association helped secure funding
- “Pioneer” VNS patent issued to Zabara October 1987
- Funding of $1 million with VCs December 1987
- Design completed, IDE and IRB approvals in September 1988
- First implant in November 1988; 11 months after funding
- First two patients were huge successes
- FDA Approval seven years later in 1997
  - CE Mark 1994; Japan MHLW 2010
VNS Seizure Reduction
16 years commercial experience

Cost Effectiveness

VNS Therapy Reduces Health Care Costs

- Non-adherence in 26% of patients taking AEDs is a big problem, resulting in a 3-fold increase in the risk of death and a 76% increase in inpatient days.\(^1\)
- VNS Therapy has a positive effect on both the utilization of health care services and time spent on Epilepsy related tasks for patients with refractory Epilepsy.\(^2\)
- Recent Emory study showed VNS “break even” at approximately 18 months.\(^3\)

VNS Therapy significantly reduces Epilepsy-related medical costs by reducing patient visits to health care facilities.

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3 Helmers S, et al. Characteristics and Clinical and Economic Outcomes in MEDICAID Patients Receiving Vagus Nerve Stimulation Therapy for the Treatment of Refractory Epilepsy. AES Abstract 2.211. 2010
Arrived in 2007 with Cyberonics losing $50 million per year, $100 million debt and a no coverage decision for depression

Set 5 year goals

- Focus on epilepsy, an underserved population
- Eliminate debt
- Double digit yearly revenue growth
- Double digit profit growth

“Cyberonics must be financially strong to deliver therapy to patients.”
VNS Epilepsy Market (U.S.)
15% of refractory patients have been treated

U.S. Population: 307M

U.S. VNS indication for use restricted to:
- Partial seizures isolated to one area of the brain
- Patients over age 12

PREVALENCE
2.7M in U.S. suffer from Epilepsy

INCIDENCE
125,000 new patients diagnosed each year

400,000 Potential VNS Therapy Candidates

~ 57,000 Patients Implanted

~ 3,700 Estimated new patients implanted in FY12

15,000 New Potential VNS Therapy Candidates

1 Source: US Census Bureau
2 Source: CDC
3 Source: NIH
Sales and Operating Income FY13

*Mid-point guidance

FY14 Guidance
Sales = $279m - $283m
OI = $85m - $88m

*Net Sales
Income from Operations
Loss from Operations

$ in Millions

FY08 FY09 FY10 FY11 FY12 FY13 FY14 *

$0 $(25,000) $25,000 $50,000 $75,000 $100,000 $125,000 $150,000 $175,000 $200,000 $225,000 $250,000 $275,000 $300,000
Operating Income increased year-over-year
Cash and Short-Term Securities Position increased to $136 million

- $39 million growth in cash, cash equivalents, and short-term securities over last year
• Leader in medical devices for epilepsy
• Headquarters: Houston, Texas
• International Sales: in ~70 countries
• Employees: ~570
• Patients: ~68,000 since 1988
• Total device implants: ~100,000

Net Sales:
FY 2013 = $254 Million
Recent *data* reinforces VNS clinical efficacy and cost effectiveness

Continued progress in **U.S. market development**

Increasing efforts in key **International** markets

**Product development** key milestones:

- **AspireHC™** high capacity generator
  - Launched in US; EU in limited commercial release

- **AspireSR™** seizure response generator
  - EU E-36 trial completed enrollment
  - US E-37 IDE trial enrolling

Outlook governed by Safe Harbor Statement.
Current Epilepsy Product Development Focus

Enhance the effectiveness of VNS Therapy by:

• Closing the loop on therapy (AspireSR)
  • Seizure Detection
  • Responsive Stimulation
  • Automatic Magnet Mode

• Improving stimulation algorithms
  • New Stimulation Paradigms

Providing new device options for patients

• Mobile Healthcare
  • ProGuardian™
  • Remote Patient Care

Above from Wang et al. J of the Neurological Sciences 2009.
Other Cyberonics Neuroscience Initiatives

- Other VNS Therapy indications
  - Depression
  - Chronic Heart Failure (CHF)
- Other neuroscience opportunities
  - ImThera for OSA

21 agreements with 16 partners
Mapping Vagus Brain Projections
Potential New Therapies
Vagal Projections to the CNS
c-Fos and delta-FosB tracing

INS = insular cortex; ILC = infralimbic cortex; PBN = parabrachial nucleus; LC = locus coeruleus; DRN = dorsal raphe; NTS = nucleus tractus solitarius; AMB = nucleus ambiguus; VLM = ventrolateral medulla; IML = intermediolateral cell column

Courtesy of Thomas Cunningham, PhD, University of Texas Health Science Center at San Antonio
Vagus connections and Brain projection map

Hermann et al 2008
Derived from MRI images
Treatment Resistant Depression (TRD) Therapy Development

- FDA approval July 2005
- CMS non-coverage decision May 2007; meeting with CMS April 2008 to discuss TRD direction
- Developed and funded post-FDA approval studies to demonstrate additional efficacy

- Evidence to support Medicare coverage of VNS for TRD
  - D-21 randomized trial; four recently published papers, 60-month follow-up summary of TRD registry
  - Meta analysis of clinical studies’ Medicare claims database analysis
  - APA updated treatment guideline

* US CMS Declined to Review non-coverage decision May 2013
VNS is protective against sudden death in dogs with healed myocardial infarction (Vanoli 1991)

Terry/Adkins 2003 patent on VNS for CHF

**CHF Pilot Study** sponsored by BioControl (DeFerrari 2010)

Cyberonics completed enrollment in 20 patients study; Boston Scientific enrolling in pilot study; Medtronic invests in BioControl

Vagus stimulation reduces infarct size and inflammatory response after myocardial ischemia in rats (Calvillo 2011)
• N = 32

• Heart rate: 82 > 76  p<0.07

• Improved New York Heart Classification  p<0.001

• Left ventricular ejection fraction: 22.3 > 28.7  p < 0.0003

• 6 minute walk test: 411 > 471  p < 0.0014

• Minnesota QOL : 49 > 32.0  p< 0.0001
Vagus is a key part of the immune/inflammation system

- Vagal afferents signal tissue injury to the brain
- Brain send signals to release cytokines to fight the injury
Wiring of the cholinergic anti-inflammatory pathway
• Sepsis Rat Study: Kevin Tracy, M.D (Nature 2000)

• Rheumatoid arthritis: Four European centers sponsored by Setpoint Medical (ClinicalTrials.org); Setpoint recently close a $27 million financing round

• Crohn’s disease: University of Grenoble (ClinicalTrials.org)

• Reduction of inflammatory response to abdominal surgery: University of Leuven (ClinicalTrials.org)

• *Inflammation has been found to be a factor in epilepsy, CHF and brain injury*
Interest is building for VNS Therapy as possible therapy in brain rewiring and functional recovery for traumatic brain injury (TBI) and stroke.

- Danielsson Doctorial published on Adult Neurogenesis 1991
- Naritoku patent on VNS for TBI 2000
- Danielsson provisional application on VNS for Stroke 2008
• Rat Study: Improved functional outcomes in rats at 14 days after percussion TBI  (Smith 2006)
  – beam walk, skilled fore arm reaching, locomotor placing, fore arm flexion, Morris water maze, therapy initiated either 2 or 24 hours after injury

• Rat Study: Therapy delayed 14 days; improved functional outcomes at 28 days after percussion TBI (Tan report 2009)

• Pilot Study Enrolling: VA grant sponsored pilot study at NYU/VA (Shi 2013)
VNS for Stroke Recovery

- **Electrical Stimulation Improves Stroke recovery**
  - Three papers of improved stroke recovery with **tDC** (Lindenberg 2011)
  - One paper of improved stroke recovery with **TMS** (Weiduschat 2011)
  - One Pilot study of *sphenopalatine ganglion (SPG)* stimulation for stroke; pivotal study (World Stroke Congress Poster 2008)


- **Three MOA** papers published (Cheyuo 2011, Mravec 2010, Otanni 2009)
  - Increasing production and survival of New Stem Cells (Revesz 2008)
  - Decreasing Inflammation and Cell Death (Majoie 2010)
  - Increasing amount of Norepinephrine
    - **Eight** of ten studies showed improved stroke recovery with **amphetamines** (Martinsson 2003)

- Increasing amount of Serotonin
  - **One** paper of improved stroke recovery with **Fluoxetine** (Chollet 2011)
Pilot Study Enrolling 20 patients: University of Glasgow hope to assist patients who have suffered from a stroke to overcome the ensuing physical problems by directly stimulating their brains in the hope that they will “rewire” themselves.

Microtransponder has sponsored this pilot study.
Tinnitus Pilot Study

Percutaneous Stimulation

• Vagus innervates the tragus part of the ear

• VA spends $1.5 billion on tinnitus disability (American Tinnitus Society)

• Encouraging Pilot study results reported by MicroTransponder (Lehtimaki 2012)
  – 40% responders in Tinnitus Handicap Inventory (THI)
  – 70% responders in Tinnitus Handicap Questionnaire (THQ)

• Theory – Stimulation needs to be paired with therapy

• Grants – Awarded by NIH and the DOD for additional pilot studies of implantable VNS to treat tinnitus
External VNS Stimulation (tVNS)

• Potential disadvantages
  • Implantable devices do not work on all patients
    – Muscle stimulation, pain
    – More variables with placement, nerve activation and compliance for clinical studies

• Theoretical Advantages
  – Lower cost clinical trials
  – Lower cost therapy
  – Screening method pre-implant
External Vagus Stimulators

cerbomed

ElectroCore
• Epilepsy – 10 patient study (Stefan 2012)
  Seizure reduction in 5 of 6 patients

• Pain – 48 patient study, double blind randomized (Busch 2012)
  – an increase of mechanical and pressure pain threshold and a reduction of mechanical pain sensitivity

• Depression – 37 patient randomized study (Hein 2012)
  – Significant improvement in Beck Depression Inventory (BDI) score
Electrocore tVNS
Promising Pilot Study Results

- Special waveforms to stimulate cervical vagus without pain or muscle stimulation
- Encouraging Pilot Study Results
  - Migraine - 2/3rds of mild migraine patients symptom free 2 hours post treatment (N = 27) (Podium presentation AAN 2013)
  - Cluster headaches - Reduced severity and frequency (Marin presentation EHMTIC 2012)
  - Asthma - Improvement in Forced Exploratory Volume (FEV1) and Work of Breathing (VAS) (Miner 2012)
  - Bronchial COPD - improvement in dyspnea scores
- Theory – A 90 second stimulation will rebalance the system for hours or longer
After 25 years, VNS Therapy and Cyberonics have stood the test of time

- VNS is now a standard cost effective treatment for refractory partial seizures
- Cyberonics is one of the premier medical device companies that employs over 580 people
- Understanding of the vagal brain circuits and parasympathetic system has increased
- Twelve promising VNS therapies and technologies are in clinical investigation
* It is a life changing device. In the Jewish Torah it talks about "Tikun Olam" which means we have to take care and mend the world. You and the others involved in the VNS have certainly fulfilled that. Thanks again and always - S. F.

From a Mother whose daughter has been seizure free with VNS Therapy