New Therapies Pipeline Update

Epilepsy Pipeline Update - 2014
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Patricia Osborne Shafer RN, MN

Associate Editor, epilepsy.com,
Epilepsy Foundation

Epilepsy Nurse Specialist
Beth Israel Deaconess Medical Center, Boston MA
Outline

• Changing concepts
• Causes
• Medications
• Devices
• Medical Marijuana
• Health and Wellness
• Advocacy and Participation
The Pipeline: What is it?

• Drugs, devices, diagnostics, dietary and complementary/alternative therapies

• **Our Future**: Wellness, better lives and an end to seizures and side-effects

• **Our Mission**: New therapies in a timeframe that matters for people living with epilepsy *today*
A View of the Pipeline

- [www.epilepsy.com/pipeline](http://www.epilepsy.com/pipeline)
- Gives visibility to new therapies, their sponsors and their stage of development
- Provides a picture and a way of tracking new ideas and progress
New Therapies Pipeline

The unique mission of the Epilepsy Therapy Project, an initiative of the Epilepsy Foundation, is to accelerate new therapies for people living with epilepsy and seizures. As a reflection of our commitment and as a service to the community we are pleased to provide here the pipeline of epilepsy therapies in various stages of development.
## The Impact

<table>
<thead>
<tr>
<th>Group</th>
<th>Pipeline</th>
<th>EF/ETP Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>49</td>
<td>25</td>
</tr>
<tr>
<td>Drug Delivery</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Dietary Supplement</td>
<td>1</td>
<td>1</td>
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<tr>
<td>Therapeutic Devices</td>
<td>9</td>
<td>8</td>
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<tr>
<td>Detection &amp; Prediction</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Diagnosis</td>
<td>12</td>
<td>7</td>
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<tr>
<td>Safety Devices</td>
<td>2</td>
<td>1</td>
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<tr>
<td><strong>Marketed 2013</strong></td>
<td><strong>14</strong></td>
<td><strong>4</strong></td>
</tr>
<tr>
<td>Dormant Projects</td>
<td>19</td>
<td>7</td>
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<tr>
<td><strong>TOTALS</strong></td>
<td><strong>123</strong></td>
<td><strong>60</strong></td>
</tr>
</tbody>
</table>
Examples of New Therapies Helping People Now

# 1: Visualase

MRI-Guided Laser Ablation Technology for Minimally Invasive Neurosurgery
Therapies Helping People Now

# 2: Smartwatch by Smart Monitor
Therapies Helping People Now

# 3: SAMi by HiPass Designs

SAMi pairs a sophisticated camera that can see in complete darkness with an easy to use app running on your Apple iPhone or iPod Touch.
Therapies Helping People Now

# 4. Monarch eTNS from Neurosigma
Changing Concepts

- Epilepsy, seizure disorder, epileptogenesis
- Antiepileptic drugs (AED), antiseizure drugs (ASD)
- Disease or disorder
New Definition of Epilepsy

• At least 1 unprovoked seizure and are likely to have further seizures.

• Reflex seizures, provoked by a specific situation.

• Diagnosed with an epilepsy syndrome
A disorder is “an abnormal physical or mental condition”

A disease is “an illness that affects a person” or a “condition that prevents the body or mind from working normally”
Causes of Epilepsy

- **Genetics** – complex relationships, cause of some devastating or rare epilepsy syndromes, may help determine responsiveness to treatment
- **Traumatic brain injury** – new insights?
- **Inflammation** – new options for therapy?
- **Comorbid conditions** – consequences or causes?
Ideal Treatment

- Works in people with refractory epilepsy
- Few to no side effects
- Can be given once a day at most
- Does not interact with other medications
- Can be easily started and maintained
- Available in many formulations
- Affordable and available
- Has a logical way of working in the brain
Drugs for Daily Use

- **Aptiom®** (eslicarbazepine acetate), *Sunovion*
- **Fycompa®** (perampanel), *Eisai*
- **Qudexy XR®** (extended release topiramate), *Upsher-Smith*
- **Oxtellar XR®** (extended-release oxcarbazepine), *Supernus*
- **Trokendi XR®** (extended-release topiramate), *Supernus*
Fycompa (Perampanel)

- First medicine to works on brain cells that excite or stabilize cell membranes
- Inhibits excitatory chemical in the brain (AMPA)
- Approved for add-on treatment in partial seizures first
  - ? Generalized convulsions next
Immediate vs Slow Release

Risk of side effects

Risk of seizure breakthrough

Cloyd, 1998
Rescue Therapies

• Medicines used ‘as needed’ (prn) to treat ‘potential seizure emergencies’
  – Acute repetitive seizures or clusters
  – A change in number, length or pattern of seizures from one’s typical seizures
  – Breakthrough seizures

• Treating these seizures is not the same as emergency treatment. The goal is to prevent true seizure emergencies
Frequency of Seizure Emergencies

Each year,

- 90,000-165,000 patients with acute repetitive seizures*
- 368,000 patient visits to emergency rooms**
- Status epilepticus
  - 237,900 episodes annually***
  - 1%–8% of all hospital admissions
  - First seizure in 12% of patients

(Cloyd, 2014: *Personal communications, S. Shinnar, ** Scott Levin Audit, *** Adjusted to 2009 US population; Delorenzo, Status Epilpeticus-Mechanisms and Management, 2006)
Rescue Therapies - What’s New?

- Buccal/Sublingual
  - Midazolam
- Intramuscular & Subcutaneous
  - Midazolam
  - Diazepam (autojector stopped)
- Intranasal
  - Diazepam, Midazolam
Midazolam

- A form of benzodiazepine
- Faster acting, better response than Diastat suggested by research
- Can be given under the tongue, between cheek and gum, or into nose

(Cloyd, 2014)
Buccal Midazolam Products

**Epistatus**
- 10 mg/ml-5ml bottle
- 4 1ml syringes
- Specialty Products (UK)

No controlled trials demonstrating safety and efficacy

(Cloyd, 2014)
IN Midazolam vs IV Diazepam

- Study on midazolam nasally and diazepam IV in children with prolonged seizures
- 47 children from 6 months to 5 years
- Main outcomes: Time from arrival at hospital to drug administration & time to stopping seizure
- Observation period = 60 minutes

(Cloyd, 2014)
Midazolam vs Diazepam


Intranasal midazolam 0.2 mg/kg
Intravenous diazepam 0.3 mg/kg

Time (minutes)

Non-responses (%)
Intranasal Diazepam Formulations

Bioavailability
Solution = 97%
Suspension = 70%

# of Subjects = 24, healthy volunteers

Suresh, Cloyd et al, Epilepsy Research, 2013
## Development of New Rescue Therapies

<table>
<thead>
<tr>
<th>Route</th>
<th>Drug</th>
<th>Sponsor</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN</td>
<td>Diazepam</td>
<td>Neurelis</td>
<td>Phase I completed</td>
</tr>
<tr>
<td>IN</td>
<td>Midazolam</td>
<td>Neuronex/Acorda</td>
<td>NDA resubmission in progress</td>
</tr>
<tr>
<td>IN</td>
<td>Midazolam</td>
<td>Upsher Smith</td>
<td>Phase III</td>
</tr>
<tr>
<td>IN</td>
<td>Clonazepam</td>
<td>Jazz</td>
<td>Development discontinued</td>
</tr>
<tr>
<td>IN</td>
<td>Water-soluble BZD prodrugs</td>
<td>University of Minnesota</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Alprazolam</td>
<td>Alexza Pharmaceuticals</td>
<td>Pre-clinical (for epilepsy)</td>
</tr>
<tr>
<td>IM</td>
<td>Diazepam</td>
<td>King/Pfizer</td>
<td>Phase III, Development suspended</td>
</tr>
<tr>
<td>IM</td>
<td>Midazolam</td>
<td>Meridian/Pfizer</td>
<td>Phase III completed</td>
</tr>
<tr>
<td>SQ</td>
<td>Diazepam</td>
<td>Xeris Pharmaceuticals</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>Buccal</td>
<td>Midazolam</td>
<td>Specialty Products</td>
<td>Marketed in selected European countries</td>
</tr>
<tr>
<td></td>
<td>Epistatus</td>
<td>ViroPharma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Buccolum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• Gene panels and personalized medicine

• Seizure detection
  – Role of EEG, video monitoring, brain mapping
  – EEG markers or predictors for seizures
Seizure Detection and Alerts
Seizure Detection and Alerts

- Repetitive shaking movements
  - Mattress - Emfit Movement Monitor, Medpage MP5
  - Watches - Smart Watch, Epilert
  - Phones - EpDetect

- Video - SAMi

- Detection devices in progress
  - Heart rate
  - Skin temperature
  - Shaking, EKG, Muscle movements
Smart Watch and Epilert

- Alerts caregivers via wireless, mobile phones, PDAs


(Anoo Nathan, Smart Watch)
• Sleep activity monitor
• Audio video recording by remote camera, sent to iPhone or iPod Touch
• Records, analyzes info
• Sends alert
ProGuardian (Cyberonics)

Chest patch
- Shake
- Pulse / EKG
- Other

(Laurie Groven, Cyberonics)
Devices for Neurostimulation

- Vagus nerve stimulation by increased heart rate (Cyberonics)
- Magnetic brain stimulation (several)
- Trigeminal nerve stimulation (Neurosigma)
- Thalamic deep brain stimulation (Medtronic)
- Responsive neurostimulation (Neuropace)
Neuropace RNS System

- Detects seizures, responds with stimulation to the brain
- Stimulator placed in the skull, up to 2 leads placed in or on the brain where seizures arise

Medical Marijuana

• Numerous animal studies, long history in epilepsy, positive anecdotal reports

• Need for randomized controlled trials

• EF advocacy for research and access

• Remarkable role of a dad, three mothers and a Doc: Jason David, Page Figi, Catherine Jacobson, Evelyn Nussenbaum and Orrin Devinsky
Medical Marijuana

- CBD vs THC
- Purity and reliability of products
- Need for lab testing
- Need for epilepsy docs and patients to stay in communication
- Challenges to research because of federal/state laws
Medical Marijuana

- https://www.youtube.com/watch?v=wQSb5laNLmY
Cannabis in the 1800’s

• **US Dispensary (1854):** neuralgia, depression, hemorrhage, pain and muscle spasm

• Ohio Medical Society Committee on *Cannabis Indica* (1860): efficacy for neuralgic pain, dysmenorrhea, hysteria, delirium tremens, mania, palsy, whooping cough, infantile convulsions, asthma, nervous rheumatism, chronic bronchitis, spasms, tetanus, epilepsy and appetite stimulation.

(Chong, 2014)
### Cannabinoids: Animal Models

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>Number of discrete conditions/models/designs</th>
<th>Dose</th>
<th>Anti-convulsant</th>
<th>No effect</th>
<th>Promotes Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>THC</td>
<td>6</td>
<td>31</td>
<td>0.25-200 mg/kg</td>
<td>61%</td>
<td>29%</td>
<td>10%*</td>
</tr>
<tr>
<td>CBD</td>
<td>2</td>
<td>21</td>
<td>1-400 mg/kg</td>
<td>81%</td>
<td>19%</td>
<td>0%</td>
</tr>
<tr>
<td>Other plant cannabinoids</td>
<td>2</td>
<td>7</td>
<td>N/A</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>CB1 receptor agonists</td>
<td>2</td>
<td>55</td>
<td>N/A</td>
<td>73%</td>
<td>18%</td>
<td>2% (7% mixed effect)</td>
</tr>
</tbody>
</table>

Whalley, 2014 American Herbal Pharmacopoeia
Survey: Parents of Children with Epilepsy on CBD>THC

- 19 children (2-16 yrs) used a CBD-enriched medical marijuana (group on Facebook)
- CBD Dose <0.5 mg/kg/day to 28.6 mg/kg/day
- THC amount reported as 0 to 0.8 mg/kg/day
- Results: 16/19 reported decreased seizures
  - 2 seizure free; 8 > 80%
  - 6 with 25-60%
- Diagnoses: Dravet syndrome (13), Doose syndrome (4), Lennox Gastaut syndrome (1), and idiopathic epilepsy (1).

(Porter BE et al, Epilepsy Behav, 2014)
# Clinical CBD Trials in Epilepsy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>INCLUSION CRITERIA Notes</th>
<th>PT #</th>
<th>DOSE TIME</th>
<th>EFFICACY</th>
<th>SAFETY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechoula m (1978)</td>
<td>TLE/TRE Groups not matched; ? AEDs, no stats</td>
<td>N=9 5 CBD 5 PLA</td>
<td>200/d x 3 mos</td>
<td>4 Rx’d: 2 Sz free, 1 better, 1 unchanged 5 Placebo: unchanged</td>
<td>No adverse events</td>
</tr>
<tr>
<td>Cunha (1980)</td>
<td>TLE/TRE &gt;= 1 TCSz/wk DB?</td>
<td>N=15 7 CBD 8 PLA</td>
<td>200-300 mg/d 3-18 wks</td>
<td>4 CBD seizure free; 1 control seizure free</td>
<td>Seizure-free: 1 placebo 4 CBD</td>
</tr>
<tr>
<td>Ames (1985)</td>
<td>Residential/M R/TRE -baseline data</td>
<td>N=12 ? CBD v PLA</td>
<td>200 mg/d x 4wks</td>
<td>No group differences</td>
<td>Mild drowsiness</td>
</tr>
<tr>
<td>Trembly (1990)</td>
<td>TRE adults Conflict of 90 paper and 92 chapter</td>
<td>N=12 ?CBD v PLA</td>
<td>PLAC x 6 mos, CBD 300/dy x 6 mos</td>
<td>No group diff on seizures or cognitive-behavior tasks</td>
<td>No data</td>
</tr>
</tbody>
</table>

(Chong, 2014)
Epidiolex (98% CBD) Studies

- Open-label study of children and young adults with TRE – Dravet, LGS, Focal epilepsy, CDKL4, etc,
- 6 sites (NYU, UCSF, Lurie Children’s, MGH, CHOP, Great Ormond St)
- Orphan drug indication approved by FDA for Dravet and LGS
- Randomized trial starting (Chong, 2014)
Summary

• Research suggests medical marijuana may be viable therapy

• Different strains of cannabis have different levels of THC & CBD

• Power of parent advocates

• Regulatory and legal burdens
Health and Wellness: Exercise, stress and wellness

- Recognized as important throughout history of epilepsy
- Incorporated into nursing care for years
- Value highlighted in numerous forums
- Underutilized
- New Health and Wellness Institute of the Epilepsy Foundation
Dietary Therapies

• Began in early 1900’s
• More popular use since 2000
• Expanded options and research in past 10 years
  – ? Role of improved nutrition in general
• Charlie Foundation, EF/ETP key role
Ketogenic Dietary Therapies

- Classic Ketogenic Diet
- Modified Ketogenic Diet
- Modified Atkins Diet (MAD)
- Low Glycemic Index Treatment (LGIT)
Ketogenic Diets

- For people who continue to have seizures after trials of 2-3 medications
- Helpful in some epilepsy syndromes such as,
  - Infantile spasms
  - Doose
  - Dravet
  - Tuberous sclerosis
  - Rett
  - Lennox Gasteau
- Certain metabolic conditions (Zupec Kania, 2014)
Dietary Therapies

• All require medical supervision
• Ketogenic diet
  – 70 to 90% fat, 3% carbs,
  – Best for children, people with tube feedings
• Other diets
  – 66 to 70% fats, 15-18% carbs
  – More flexible for use with all ages
What is coming: The Near

- GW Pharma
  - Epidiolex
- Medical Marijuana
  - Charlotte’s Web and others
- Cyberonics
  - Responsive VNS
  - Progardian Rest: night time seizure detection
What is coming: The Not So Far

- Insero: HuperzineA for Dravet, partial sz
- Brabant Pharma: Fenfluramine for Dravet
- Sage Pharmaceuticals:
  - Non-tolerance gaba, use Dravet, status ep
- UCB - Brivaracetam
- Empatica:
  - Embrace autonomic and sz detector
- Brain Sentinel: EMG based sz detection
- Transcranial Magnetic Stimulation
The Far But Visible

- Gene therapies
- Cell therapies
- More personalized medicine informed by genetics and biomarkers
- New devices
Role of Advocacy and Our Community

• Dietary Therapies
• Health and Wellness
• Diagnostic and Seizure Detection Devices
• Medical Marijuana and other Nontraditional Therapies
Our Community and ETP/EF

- A key driver of the Pipeline - generating ideas, participating in research, providing financial support
- Can drive the Pipeline forward
- Progress and better lives depends on each and every one of us!
The Rare Epilepsy Network (REN) PPRN is an initiative created by and for patients with rare epilepsies and their families.

Designed to provide patients and their families opportunities to participate in research.

Goals:

- Build patient-centered and patient-driven data base.
- Improve lives and quality of care for people with rare epilepsies.
Seven Rare Epilepsy Groups

• Drove the development of the proposal.
• Represented patient-driven work.
• Recruited the Epilepsy Foundation, RTI, and Columbia to help with the work.
• Have been actively involved in every aspect of the PCORI project.
<table>
<thead>
<tr>
<th></th>
<th>Rare Epilepsy Disorder</th>
<th>Cause</th>
<th>Approximate number in U.S.</th>
<th>Approximate new cases annually in U.S.</th>
<th>Male : Female ratio</th>
<th>Minorities represented</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>Aicardi</strong></td>
<td>Genetic</td>
<td>900</td>
<td>40</td>
<td>0:1</td>
<td>All</td>
</tr>
<tr>
<td>2</td>
<td><strong>Dravet</strong></td>
<td>Genetic</td>
<td>5,000</td>
<td>125</td>
<td>1:1</td>
<td>All</td>
</tr>
<tr>
<td>3</td>
<td><strong>Dup15Q</strong></td>
<td>Genetic</td>
<td>1,200</td>
<td>50</td>
<td>2:1</td>
<td>All</td>
</tr>
<tr>
<td>4</td>
<td><strong>Hypothalamic Hamartoma</strong></td>
<td>Unknown</td>
<td>750</td>
<td>30</td>
<td>2:1</td>
<td>All</td>
</tr>
<tr>
<td>5</td>
<td><strong>Lennox-Gastaut Syndrome</strong></td>
<td>Unknown</td>
<td>34,000</td>
<td>unknown</td>
<td>2.4:1</td>
<td>All</td>
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<tr>
<td>6</td>
<td><strong>Phelan-McDermid Syndrome</strong></td>
<td>Genetic</td>
<td>1,200</td>
<td>unknown</td>
<td>1:1</td>
<td>All</td>
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<tr>
<td>7</td>
<td><strong>Tuberous Sclerosis</strong></td>
<td>Genetic</td>
<td>50,000</td>
<td>667</td>
<td>1:1</td>
<td>All</td>
</tr>
</tbody>
</table>
• The Future
  ✷ Working toward continued funding
  ✷ Building a sustainability plan for an EF Rare Epilepsy Institute
    • Education
    • Social networking
    • Research
  ✷ Other goals
    • Endowments
    • Partnerships with relevant organizations
Empowerment – Hope - Help

• Take charge

• Join with us

• End epilepsy, seizures and Sudep
Stronger Together

Wellness & Epilepsy Conference
An Epilepsy Foundation of Michigan Feature Program