Essential Tremor 2016
A look into the pipeline

Dietrich Haubenberger
NINDS / NIH
Overview

• Clinical Trials
  • Treatment-development pipeline
  • The old and new kid on the block: ET surgery
  • What makes ET therapies successful?

• Understanding ET – challenges and future directions
Disclaimer

• This talk includes discussion of treatment approaches, which are not FDA approved.

• Mentioning of investigational treatments are no endorsement neither by me nor the NIH.

• I consult with pharmaceutical and biotechnology companies for the development of pharmaceuticals and devices to diagnose and treat tremor.

• All this is done as part of my official duty at NIH, and I do not receive any honoraria or other compensation.

• All information presented in this talk is public information.
In the pipeline: Octanoic Acid

• Metabolite of long-chain alcohol 1-octanol
• Effective in the ET animal model
• Safe in patients with ET in a single low dose (4 mg/kg)
OA dose escalation study

- OA safe and tolerable up to highest dose of 128 mg/kg
Effects of OA

• Next steps:
  • Improvement of drug formulation
  • Test against placebo over longer time-frame
SAGE-547

SAGE Therapeutics Announces Results From Successful Exploratory Trial in Essential Tremor

Clinically Meaningful Reduction of Tremor Amplitude Observed in Double-Blind, Placebo-Controlled Trial

Results Support Future Development of a Daily, Chronic, Oral Treatment

Study Represents SAGE’s Second Successful Signal-Finding Study

Conference Call Scheduled for Sept. 3rd at 8:30 a.m. ET

• Drug developed for Status epilepticus
• Presumed effect on GABA receptor in the brain
Results of trial

• Not (yet?) published in medical literature
• Company presented data at American Academy of Neurology annual meeting in April 2016
• Per company (http://www.abstractsonline.com/pp8/#/4046/presentation/5963):
  • Double blind, placebo controlled, cross-over trial in 25 patients with ET
  • Drug given as infusion over 12 hours, escalating dose
  • Effects measured by accelerometry, TETRAS
  • Results:
    • “Significant reductions in kinetic tremor scores” in accelerometry
    • High-dose side effects: sleepiness, fatigue, dizziness, hypotension
  • 17 subjects came back for open label infusion after double-blind study
Other targets: AMPA receptor

ClinicalTrials.gov
An Efficacy/Safety Study of Perampanel for Reducing Essential Tremor

This study is ongoing, but not recruiting participants.

Sponsor:
VA Greater Los Angeles Healthcare System

Information provided by (Responsible Party):
Adrian Handforth, MD, VA Greater Los Angeles Healthcare System

ClinicalTrials.gov Identifier:
NCT02668146

First received: October 28, 2015
Last updated: September 8, 2016
Last verified: September 2016

Purpose
Obtain information on whether the medication Perampanel reduces tremor in people with essential tremor and is well-tolerated.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential Tremor</td>
<td>Drug: Perampanel</td>
<td>Phase 2</td>
</tr>
<tr>
<td></td>
<td>Drug: Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Reduce neuronal hyperexcitation by targeting glutamate activity at postsynaptic AMPA receptors

www.epilspsyu.com
Limb cooling

Electrophysiological Study of the Effects of Limb Cooling on Essential Tremor

This study has been completed.

Sponsor:
Mayo Clinic

Information provided by:
Mayo Clinic

ClinicalTrials.gov Identifier:
NCT01093027

First received: March 24, 2010
Last updated: December 14, 2012
Last verified: December 2012

Purpose

To determine the effects of upper limb forearm cooling on Essential Tremor upper limb tremor using a more practical method of limb cooling through a forearm cold pack.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
</tr>
</thead>
</table>
| Tremor    | Other: 15 - 30  
            | Other: 30 - 15 |
Limb cooling

Reporting Groups

<table>
<thead>
<tr>
<th>Description</th>
<th>15 - 30</th>
<th>30 - 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>The upper limb with tremor will be cooled with 15 degrees Celsius water for 10 minutes at Visit 1 and with 30 degrees Celsius water for 10 minutes at Visit 2.</td>
<td>The upper limb with tremor will be cooled with 30 degrees Celsius water for 10 minutes at Visit 1 and with 15 degrees Celsius water for 10 minutes at Visit 2.</td>
<td></td>
</tr>
</tbody>
</table>

Participant Flow for 2 periods

<table>
<thead>
<tr>
<th>Period 1: Visit 1</th>
<th>15 - 30</th>
<th>30 - 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARTED</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>COMPLETED</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>NOT COMPLETED</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Period 2: Visit 2</th>
<th>15 - 30</th>
<th>30 - 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>STARTED</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>COMPLETED</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>NOT COMPLETED</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Measured Values

<table>
<thead>
<tr>
<th>Number of Participants Analyzed [units: participants]</th>
<th>15 - 30</th>
<th>30 - 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Tremor Amplitude [units: cm/s^2] Mean (Standard Deviation)

<table>
<thead>
<tr>
<th>Visit 1</th>
<th>127 (50)</th>
<th>104 (44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 2</td>
<td>150 (73)</td>
<td>100 (58)</td>
</tr>
</tbody>
</table>
Limb Cooling in Essential Tremor

This study is currently recruiting participants. (see Contacts and Locations)

Verified September 2016 by University of Florida

Sponsor:
University of Florida

Information provided by (Responsible Party):
University of Florida

ClinicalTrials.gov Identifier:
NCT02067702

First received: February 14, 2014
Last updated: September 13, 2016
Last verified: September 2016

Procedure: Limb Cooling Assessment of ET

The non-pharmacological treatment assessments of limb cooling will take place for the subjects which will include the upper limbs. Both clinical and physiological recordings will be measured for a difference in tremors at three different temperatures. 1)baseline assessment maintaining a normal body temperature (96-98°F). 2) at a temperature of 59°F and 3) at a temperature of 80°F for a period of 10 minutes. The clinical assessments will include the Tremor Rating Scale (TRS), Handwriting Assessment Battery (HAB) and the Functional Dexterity Test (FDT). In addition, the Bagnoli and Trigno EMG systems to record surface EMG signals from muscles and accelerometer readings.
In business news ...

Cala Health gets $18M for tremor-treating wearable

By Jonah Comstock  |  February 18, 2016

Cala Health, a stealthy startup out of Stanford University has raised $18 million according to an SEC filing. MedCityNews first spotted the story. Johnson & Johnson Development Corporation, Lux Capital and Lightstone Ventures all contributed to the round.

Cala Health hasn't sought much press and declined to comment to MobiHealthNews. But the SEC document reveals that the company was previously known as Resido Medical, which won several competitions in 2013 with a wearable device that treats hand or wrist tremors. At the time, the device was already in clinical trials.

http://www.mobihealthnews.com/content/cala-health-gets-18m-tremor-treating-wearable
A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor

W. Jeffrey Elias, M.D., Nir Lipsman, M.D., Ph.D., William G. Ondo, M.D., Pejman Ghanouni, M.D., Ph.D., Young G. Kim, M.D., Ph.D., Wonhee Lee, M.D., Ph.D., Michael Schwartz, M.D., Kullervo Hynynen, Ph.D., Andres M. Lozano, M.D., Binit B. Shah, M.D., Diane Huss, D.P.T., N.C.S., Robert F. Dallapiazza, M.D., Ph.D., Ryder Gwinn, M.D., Jennifer Witt, M.D., Susie Ro, M.D., Howard M. Eisenberg, M.D., Ph.D., Paul S. Fishman, M.D., Ph.D., Dheeraj Gandhi, M.D., M.B., B.S., Casey H. Halpern, M.D., Rosalind Chuang, M.D., Kim Butts Pauly, Ph.D., Travis S. Tierney, M.D., Ph.D., Michael T. Hayes, M.D., G. Rees Cosgrove, M.D., Toshio Yamaguchi, M.D., Ph.D., Keiichi Abe, M.D., Takaomi Taira, M.D., Ph.D., and Jin W. Chang, M.D., Ph.D.

• July 11, 2016: FDA approval
Efficacy on Tremor

(A) Mean Tremor Score over time for Sham (N=20) and FUS thalamotomy (N=56).

(B) Change in Tremor Score from Baseline to 3 Mo (%).
Efficacy on Disability

A

Disability Score

<table>
<thead>
<tr>
<th></th>
<th>FUS thalamotomy</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>3 Mo</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>12 Mo</td>
<td>5</td>
<td>10</td>
</tr>
</tbody>
</table>

B

Improvement in Disability Score (%)

<table>
<thead>
<tr>
<th>Domain</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speaking</td>
<td>20</td>
</tr>
<tr>
<td>Eating</td>
<td>60</td>
</tr>
<tr>
<td>Drinking</td>
<td>60</td>
</tr>
<tr>
<td>Hygiene</td>
<td>60</td>
</tr>
<tr>
<td>Dressing</td>
<td>60</td>
</tr>
<tr>
<td>Writing</td>
<td>40</td>
</tr>
<tr>
<td>Working</td>
<td>20</td>
</tr>
<tr>
<td>Social activities</td>
<td>80</td>
</tr>
</tbody>
</table>
Efficacy on Quality of Life

C

![Graph showing QUEST score over time for FUS thalamotomy and Sham groups](graph.png)

D

![Bar chart showing improvement in QUEST score across domains](bar_chart.png)
## Table 2. Adverse Events.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>FUS Thalamotomy (N = 56)</th>
<th>Sham Procedure (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total 1 Day 7 Days 1 Mo 3 Mo 6 Mo 12 Mo number of patients (percent)</td>
<td>Total 1 Day 7 Days 1 Mo 3 Mo 6 Mo 12 Mo number of patients (percent)</td>
</tr>
<tr>
<td>Intraprocedural sensations or events;‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head discomfort: “heat” or “pressure”</td>
<td>17 (30)</td>
<td></td>
</tr>
<tr>
<td>Vertigo: “dizzy”</td>
<td>12 (21)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11 (20)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (4)</td>
<td></td>
</tr>
<tr>
<td>Scalp tingling</td>
<td>4 (7)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Back pain</td>
<td>5 (9)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 (5)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>Pin-site pain, edema, or bruising attributable to placement of the stereotactic frame</td>
<td>17 (30)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>No adverse events</td>
<td>6 (11)</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Discomfort sensation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tinnitus</td>
<td>3 (5)</td>
<td>3 3 3 1</td>
</tr>
</tbody>
</table>
• 2015 NINDS ET Workshop Recommendations accepted for publication
Research Recommendations

• In the areas:
  • Phenomenology and Phenotypes
  • Therapies
  • Physiology
  • Pathology
  • Genetics
Recommendations Phenomenology

- Consider ET as a specific, common isolated tremor syndrome, not a specific disease
- Define ET as an isolated tremor syndrome consisting of:
  - Bi-brachial action tremor (i.e., postural or kinetic tremor)
  - Duration of 3 years or more
  - With or without head tremor or tremor in other locations
  - No other diagnostic neurologic signs (e.g., overt dystonia or parkinsonism)
- No identifiable endogenous or exogenous disturbances that could cause tremor
- Difficulty with tandem walking is permissible, but no abnormality of gait
- Consistently apply ET definition in clinical and research setting
- Prospectively collect large multi-national cohorts of individuals with ET and other isolated tremors using validated assessment tools, standardized terminology, and protocols for collection of biosamples
- Capture neurologic signs and symptoms of unknown significance to fullest extent possible to ensure unbiased phenotyping
Summary

• Many new therapeutic approaches in the pipeline
  • Targeted
  • Drugs
  • Devices

• Focused Ultrasound is the new breakthrough
  • Large effect size
  • Side effects!

• New directions or research
  • ET as syndrome with likely many different causes
  • Only large-scale, world-wide studies will give sufficient results