Advances in Treating Epileptic Seizures

Nationwide Children's
When your child needs a hospital, everything matters.℠

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College of Medicine

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Disclosures

- Research Funding – Pediatric Epilepsy Research Foundation (PERF), NIH, Stoke
- Webinar Development – Medscape
- Consulting – Greenwich Biosciences

Obectives

- Discuss evidence based data around use of cannabidiol to treat seizures
- Detail adverse effects of cannabidiol and cannabis based treatments
- Discuss other treatment recently FDA approved for LGS and Dravet

Goals of Treatment

- **According to the Epilepsy Foundation, the goal of all epilepsy treatment is to:**
  - Prevent further seizures
  - Avoid side effects
  - Make it possible for people to lead active lives

- **Individual treatment goals may include:**
  - Ability to regain/retain your driving privileges
  - Job stability
  - Academic success

Treatment Resistant Epilepsy

1/3

…of patients remain pharmacoresistant, failing to achieve sustained seizure freedom after 2 AEDs

Tx-Resistant Patients on Multiple AEDs Are Compromised

- **Increased risk for SUDEP**
- **Impairments in psychosocial, behavioral, and cognitive function**
- **More severe side effects**

Unmet Needs

Unmet Needs in Epilepsy

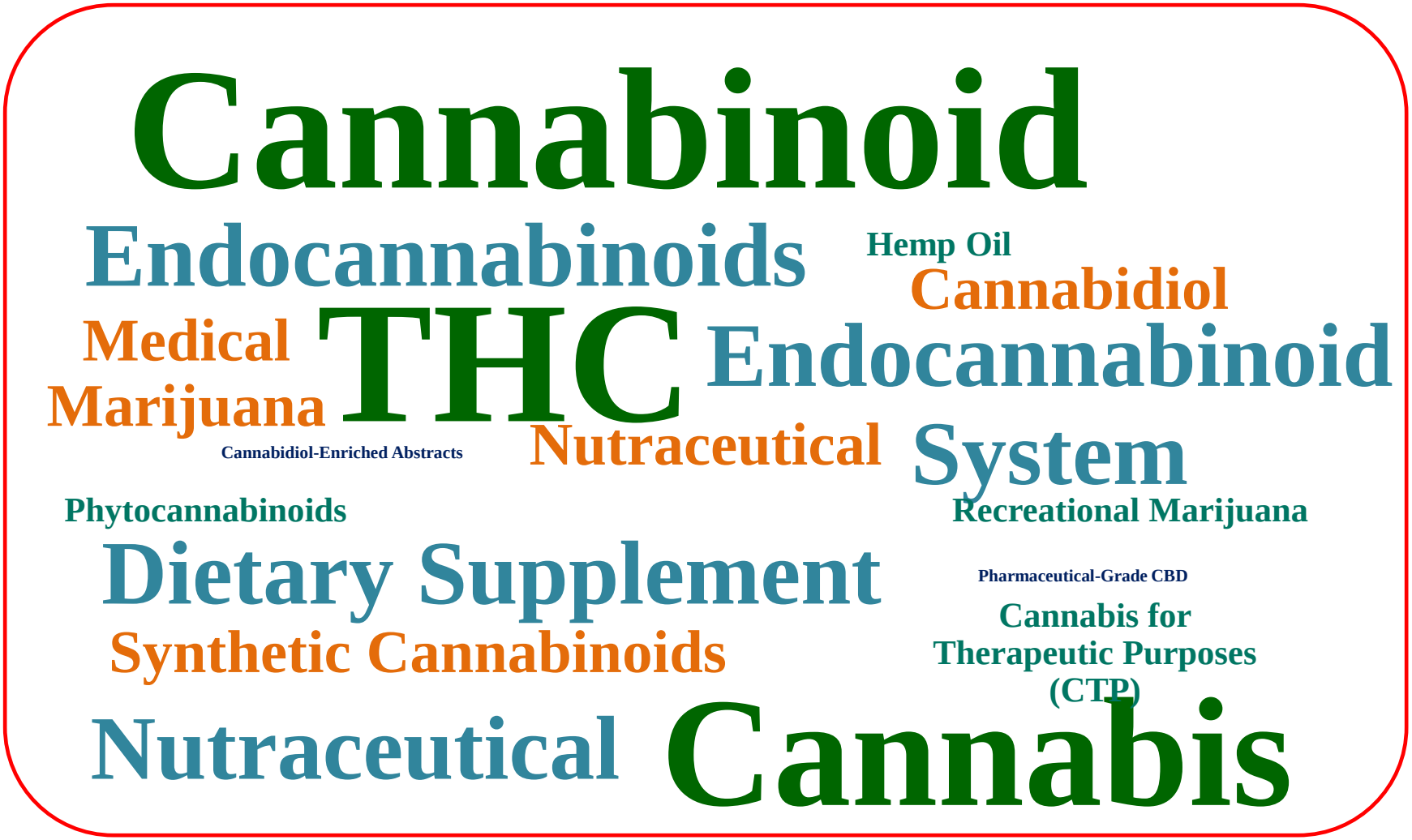
- Better identification of epileptic syndromes
- Drug-resistant epilepsy
- AEDs to prevent development of epilepsy
- Prevention, diagnosis, and management of comorbidities

Treatment Gaps with Current AEDs

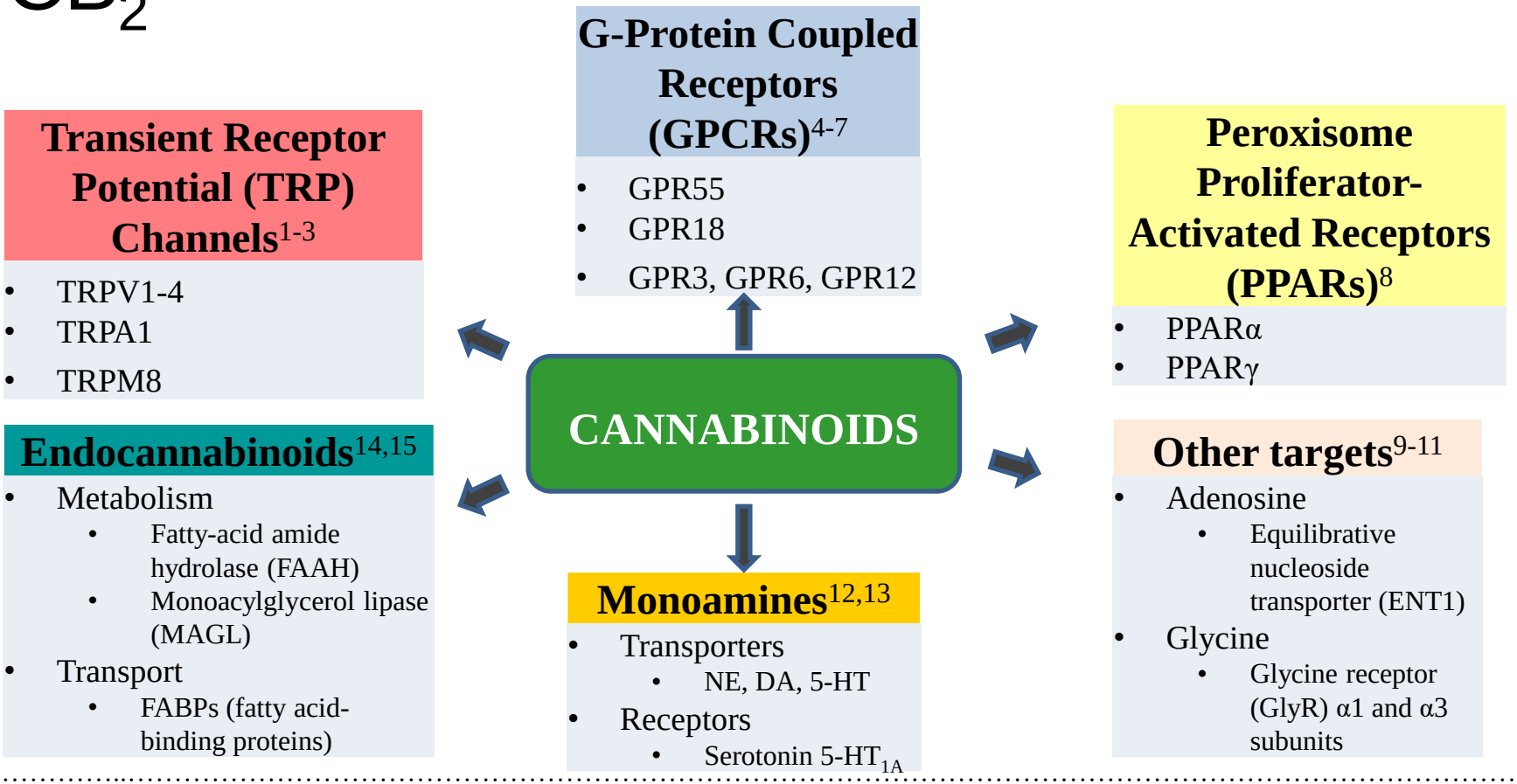
- Efficacy
- Drug interactions
- Unique mechanisms of action
- Side effects

Despite being one of the most common neurological disorders, public understanding of epilepsy is limited, presenting gaps in epilepsy knowledge, care, and education

Medical Cannabis



Cannabinoid Targets Beyond CB_1 and CB_2



Cannabidiol

- Also called CBD
- A prominent non-psychoactive cannabinoid component of *Cannabis.* It has low affinity for the cannabinoid receptor types 1 (CB_1) and 2 (CB_2)
- Plant based > 98% CBD oil based formulation (Epidiolex)

Patient #1

Open Label Study

- 137 (64%) patients were included in the efficacy analysis
  - 33 (20%) patients had Dravet syndrome and 31 (19%) patients had Lennox Gastaut syndrome. The remaining patients had intractable epilepsies
- Adverse events reported in more than 10% of patients were:
  - Somnolence (n=41 [25%])
  - Decreased appetite (n=31 [19%])
  - Diarrhea (n=31 [19%])
  - Fatigue (n=21 [13%])
  - Five (3%) patients discontinued treatment because of an adverse event
- The median monthly frequency of motor seizures was 30 at baseline and 15.8 over the 12 week treatment (50% reduction)

Long Term Data Study

- 607 patients treated
- 76% of patients remained on treatment
- CBD associated with 51% and 48% reductions in median monthly convulsive and total seizures, respectively at 12 weeks and similar at 96 weeks
- The ≥50%, ≥75%, and 100% reductions were 49%, 30%, and 7% at 96 weeks

Long Term Data Study

- 146 (24%) withdrew
  - Lack of efficacy 15%
  - AEs 5%
- Most common AEs were:
  - Diarrhea (29%)
  - Somnolence (22%)

Epidiolex Double Blind Placebo Study

Dravet Study:

- 2 to 18 years of age
- Median reduction in convulsive seizure frequency of 39% compared with 13% for placebo assessed over the entire treatment period (which included the initial dose escalation period
- Responder rate – 45%
- Safety profile similar to open label study (90% with AE compared to 78% in placebo group)
- No major adverse effects related to medication

LGS Double Blind Placebo Study

- Average age of trial participants was 16 years
- In the 20 mg/kg CBD group: the median drop seizure frequency reduction was 42% compared with 17% in the placebo group (p=0.0047)
- In the 10 mg/kg CBD group, the median drop seizure frequency reduction was 37%, compared with 17% in the placebo group (p=0.0016)
- Difference between Epidiolex and placebo emerged during the first month of treatment and was sustained during the entire treatment period
- Similar side effect profile as other studies

2nd Epidiolex Double Blind LGS Study

- 2-55 years
- The trial randomized 171 patients into two arms, where Epidiolex 20mg/kg/day (n=86) or placebo (n=85) was added to current AED treatment
- The median baseline drop seizure frequency per month was 74
- A median reduction in monthly drop seizures of 44 percent compared with a reduction of 22 percent in patients receiving placebo (p=0.0135)
- Safety profile similar to open label study (86% with AE compared to 69% in placebo group)
- No major adverse effects related to medication

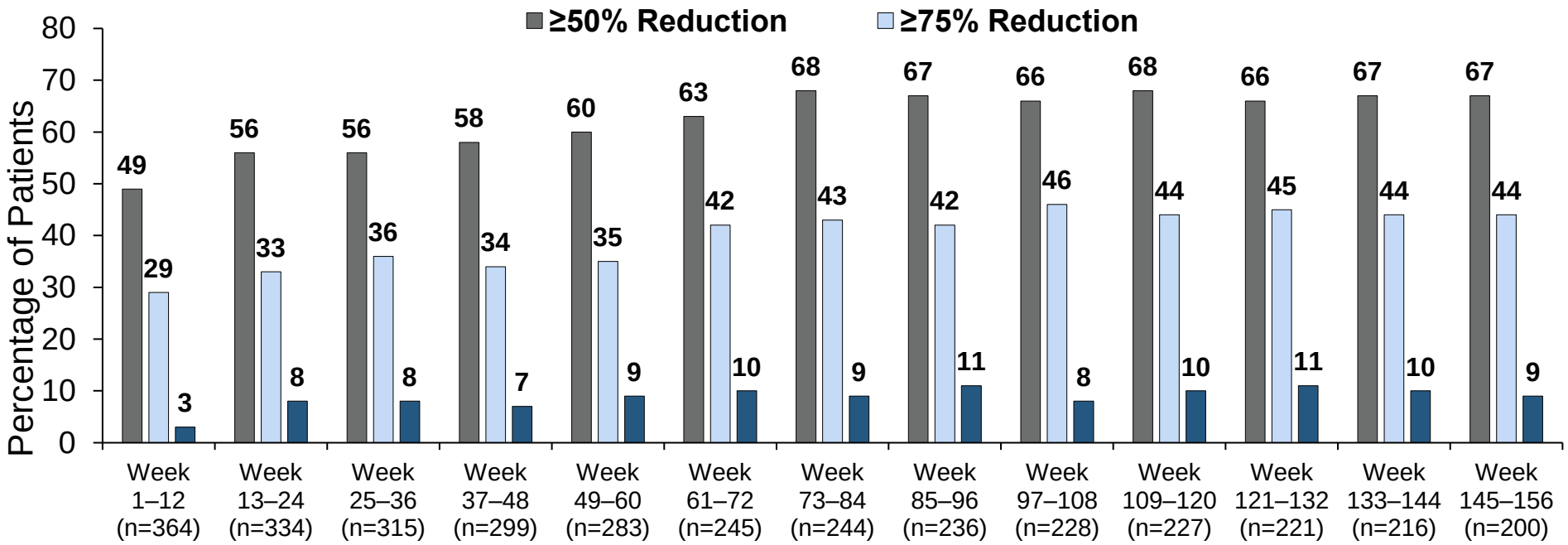
Epidiolex

- Data and studies submitted to FDA
- FDA Public Advisory Committee voted 13-0 in favor of approval
- On June 25, 2018, FDA approved Epidiolex for seizures in patients > 2 years old with LGS and Dravet syndromes
- History was made:
    - Marked the first plant based derived formulation from cannabis FDA approved for any disease state
    - First FDA approved Tx for Dravet in USA

Long Term Analysis

- Analysis of both LGS studies for long term data
- Ages 2-55 years
- 194 patients

LGS Long Term Data



How Do You Use Epidiolex In Practice?

- DEA rescheduled to schedule V originally and now not scheduled
- All states can prescribe
- Wait time anywhere from 3 days to 3 weeks
- Requires PA in most cases
- Get baseline liver function tests

Dosing

- Weight based dosing up to 25 mg/kg/day
    - No top dose
- Start at 5 mg/kg/day and increase to 10 mg/kg/day in one week
- If efficacy desired not achieved and tolerated, increase to 15 mg/kg/day and then 20 mg/kg/day
- Studies have shown efficacy and tolerability up to 50 mg/kg/day

Vernacular Cannabis Studies

Colorado Study

- Study looking prospectively at families considering oral cannabis extracts (OCE) to treat seizures
- Open label study
- OCE products were purchased by families and were not managed by providers
- Patients followed for 12 weeks after starting OCE

Results

- Twenty one patients followed
- Median age = 10 years
- Observed response rate = 24% (5/21)
- 14% (3/21) stopped use of product early due to increase in seizures
- Responder rate higher for those that moved to Colorado

Variation of Products

- Concentrations labeled for 9 subjects
- 8 used products that did not have concentrations available
- 4 used a combination of products that had labeled and unlabeled concentration

CBD Products Cannot Make Medical Claims

- Any item is considered a drug (subject to the FDA approval process) if it is intended for use in the cure, mitigation, treatment, or prevention of disease
- **February 26, 2015**: FDA issues Warning Letters to 6 vendors covering 16 CBD products, stating that the products are misbranded due to medical claims
  http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
- ***FDA tested the products and ½ of them contained no cannabinoids***; others had lower CBD content and/or higher THC content than on the label.
  http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm435591.htm
- **Update:** 8 more vendors were sent letters by FDA in **February, 2016**
  http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm484109.htm

PTL101

- Oral CBD formulation
- Made using a proprietary gelatin matrix pellet technology developed to provide for oral, high-loading, excipient-free, cannabinoid-based preparations
- The gelatin matrix is made of a 100% natural and digestible gelatin polymer that is readily soluble at body temperature
- The CBD used was derived from highly purified *Cannabis sativa* extract (> 93% CBD; < 0.2% THC), prepared

Dosing

- 50 mg initially
- A maximum dose of 25 mg/kg per day or 450 mg/day (whichever lower)
- 10 week maintenance phase

Results

- 16 patients enrolled (11 female) with 11 completing
- Withdrew:
  - 2 for worsening of seizures
  - 1 lack of compliance
  - 1 mild adverse events probably related to treatment
  - 1 withdrew consent
- Average starting dose was 15.4 ± 5.1 mg/kg, and the average dose for the 10-week maintenance phase was 13.6 ± 4.2 mg/kg

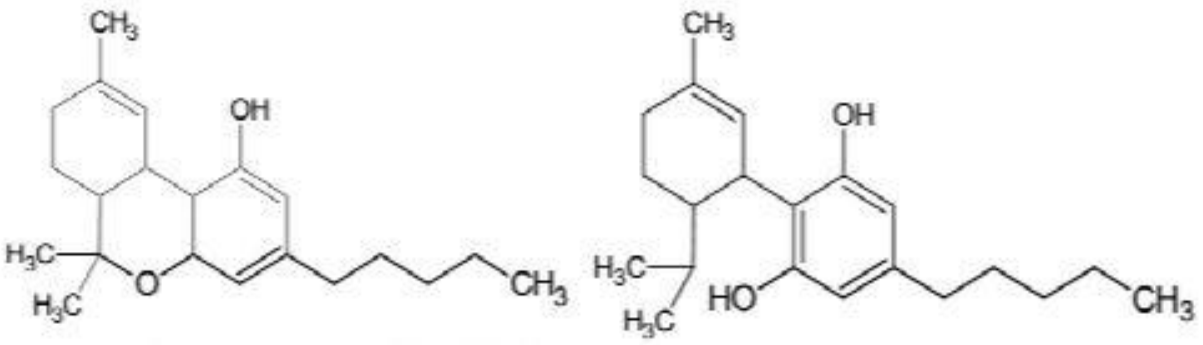
Results

- Mean 73.4 ± 24.6% and a median 81.9% reduction in monthly seizure frequency was achieved during the 12-week treatment period
- End of treatment period:
  - 9 patients (56.3%) were considered responders
  - 2 patients seizure-free at the second and third treatment periods
  - Caregiver overall impressions of seizure severity and overall improvement:
  - 82% (9 patients) reporting reduced or very much reduced seizure severity
  - 73% (8 patients) ranking the condition as either improved or very much improved by the end of the study

Adverse Events

- 36 (1.8%) were associated with at least one treatment-related adverse event, reported by eleven patients (68.8%)
- The most common effect: nervousness and sleep disturbances, each reported by 4 (25.0%) patients, followed by somnolence and increased epileptic seizures, each reported by three patients (18.8%)

What About Other THC/CBD Ratios?



CBD-Enriched Cannabis Oil in Pediatric TRE

- Retrospective review of clinical records from 4 Israeli epilepsy clinics
  - Participants
    - Children and young adults aged 1 to 18 years with TRE
    - Followed for ≥ 12 months before and > 3 months after receiving CBD
  - Study medication
    - CBD-enriched cannabis oil (CECO) -- 20% CBD: 1% THC
    - Dose: individualized based on seizure response and AEs
      - 1 to 10 mg/kg per day
      - 10 to 20 mg/kg per day

CBD-Enriched Cannabis in Pediatric TRE

Change in seizure frequency	Participants*, n (%)
Exacerbation leading to withdrawal	**5 (7)**
Reduction	
< 25%	19 (26)
25% to 50%	9 (12)
50% to 75%	**25 (34)**
75% to 100%	13 (18)

AEs	Participants, n (%)
Seizure exacerbation	13 (18)
Somnolence/fatigue	13 (22)
GI problems and irritability	5 (7)

Observed Improvements

- Behavior and alertness
- Language
- Communication
- Motor skills
- Sleep

What About THC in General?

- Likely either neutral or proactive as an anti-seizure chemical
- Broken down in liver as rest of plant
- Can have drug to drug interactions
- Likely inhibits growth of child or adolescent brain
- Needs more scientific evidence for medical use

Stiripentol (Diacomit)

- Increases GABAergic transmission and prolong GABAa receptor-mediated currents
- Can increase phenytoin, phenobarbital and carbamazepine by up to 50%
- Can also increase clobazam by up to 25%
- EU approved for Dravet syndrome (severe myoclonic epilepsy in infancy), when combined with valproate and clobazam
- The French experience in compassionate use suggests that STP might also be of benefit when combined with carbamazepine in pediatric patients with pharmacoresistant partial epilepsy

Dosing and Adverse Effects

- Common adverse effects were drowsiness, decreased appetite and nausea (can be improved by reducing dose of current AED)
- Dose range is 25 to 75 mg/kg/day BID to TID
- Available in 250 and 500 mg capsules and packets (sachets)
- FDA approved for Dravet in the US

Fenfluramine

- Phase 3 trial
  - 2-18 years of age
  - 3 arms: placebo, 0.2 mg/kg/day, 0.8 mg/kg/day
  - 6 week baseline, 2 week titration, 12 week maintenance
- Primary endpoint: mean change in convulsive seizures between placebo and 0.8 mg/kg/day
  - 0.8 mg/kg/day - 63.9%
  - 0.2 mg/kg/day - 33.7% secondary endpoint
- Secondary endpoints: responder rate, longest convulsive seizure free period (0.2 mg/kg/day)

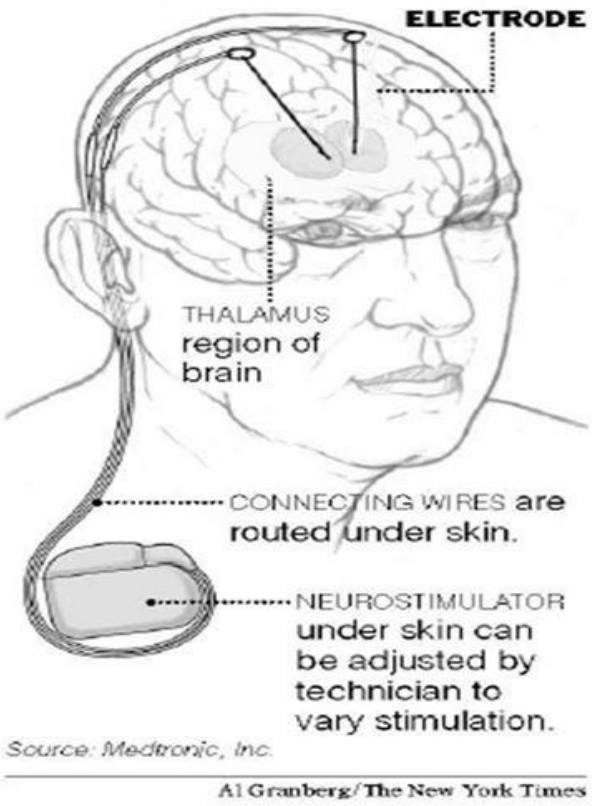
Important Items

- Need baseline ECHO and follow-up ECHO studies
- Need to enroll in REMS program
- Available from specialty pharmacy
- Contact company to help enroll into REMS program and learn how to use

DBS FDA Approval

- Add-on treatment for focal epilepsy:
  - Age 18 years and older
  - Have focal onset seizures
  - Have treatment resistant epilepsy

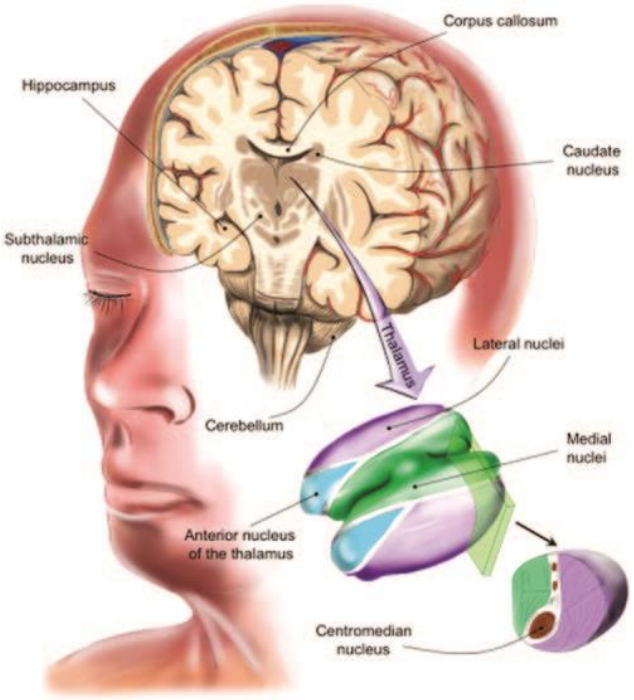
Deep Brain Stimulation



- Bilateral, open loop
- Quadripolar Leads for bipolar or unipolar stimulation
- Intermittent (cycling) stimulation

Medtronic website

Thalamus Anatomy



Anterior Thalamic Nucleus Stimulation

- Thalamic nucleus, the central relay station of the limbic system, is closely connected to the hippocampi and to extensive areas of the neocortex[1,2]
- Lesions, high frequency stimulation, microinjections of GABAergic agonists into the AN had anticonvulsant effects

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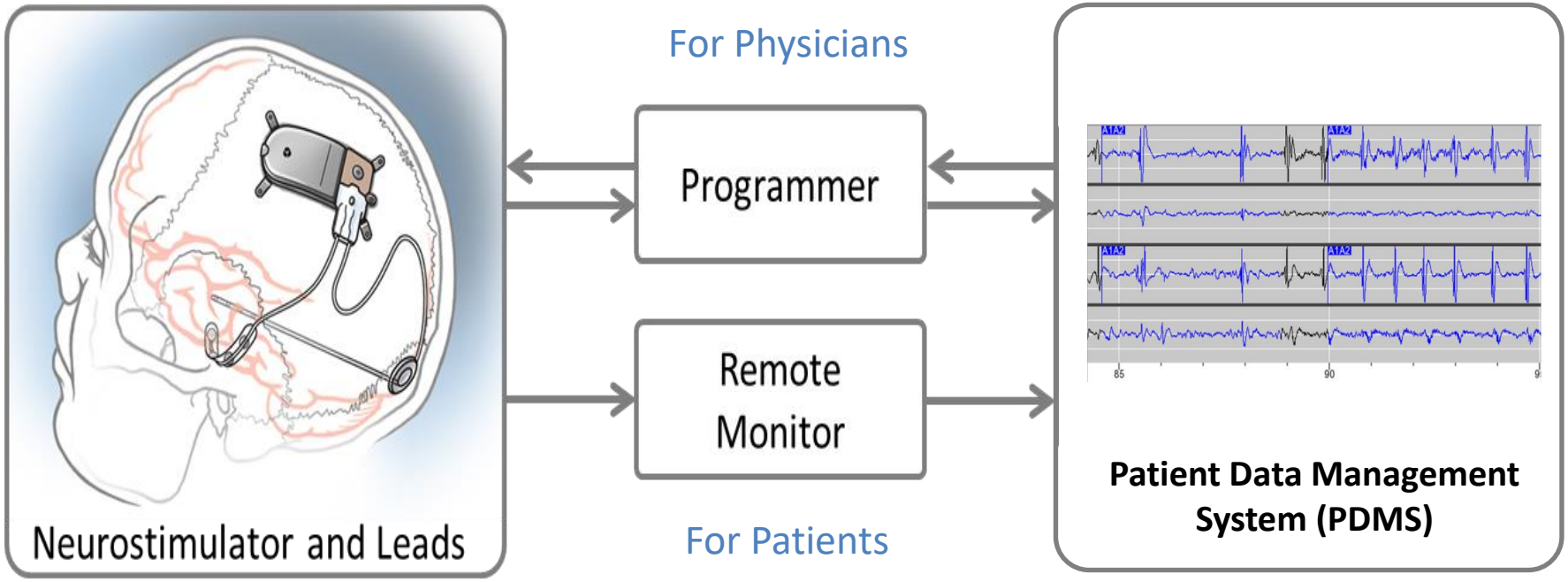
Responsive neurostimulation (RNS)

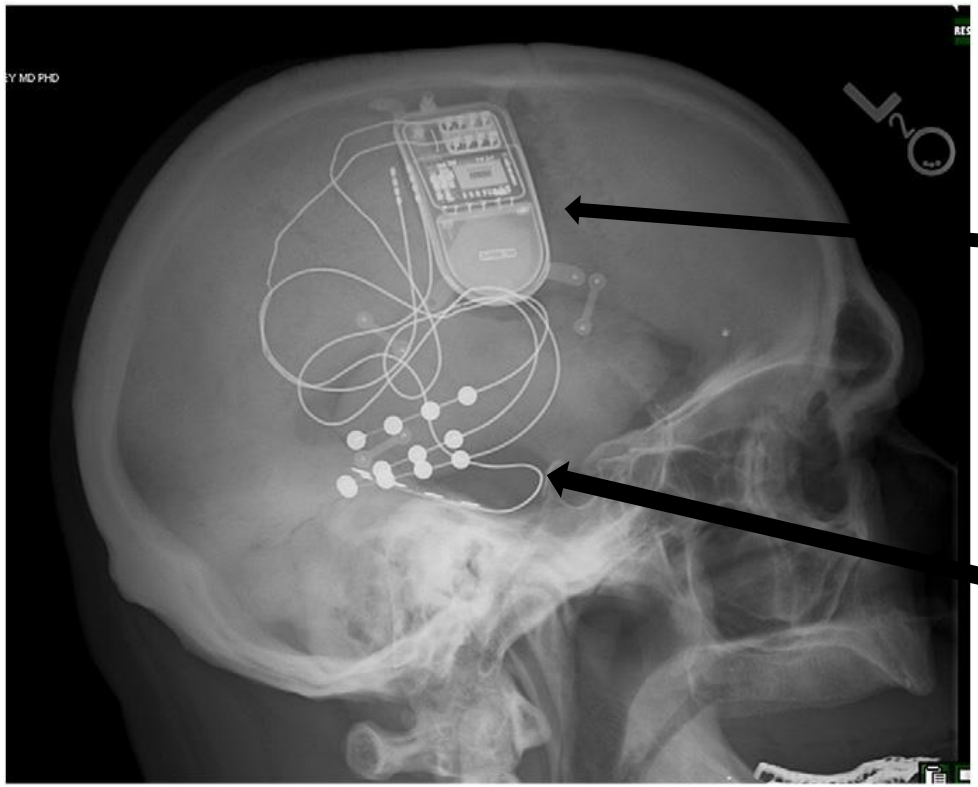
Closed loop stimulation



RNS FDA Approval

- Adjunctive therapy in reducing the frequency of seizures in individuals 18 years of age or older with partial onset seizures:
    - Who have undergone diagnostic testing that localized no more than two epileptogenic foci
    - Refractory to two or more antiepileptic medications, and currently have frequent and disabling seizures (motor partial seizures, complex partial seizures and/or secondarily generalized seizures)

Responsive Neurostimulation



generator

sensing & stimulating electrodes

Responsive Neurostimulation

- Important parameters for responsive stimulation are temporal and spatial specificity
- Early detection and accurate lead placement are important determinants of the success of RNS
    - Suggests that neurostimulation disrupts the epileptogenic network
- Seizure control improves over time
    - Suggests a neuromodulatory effect

Sun et al. *Neurotherapeutics*. 2008.
Heck CN, et al. *Epilepsia*, 2014.
Bergey GK, et al. *Neurology*, 2015

What is the Long Term Data?

Long Term Treatment

- May take time to work
- Discuss seizure reduction
- Potential for improved postictal period
- Decreased meds
- Improved attention and mood

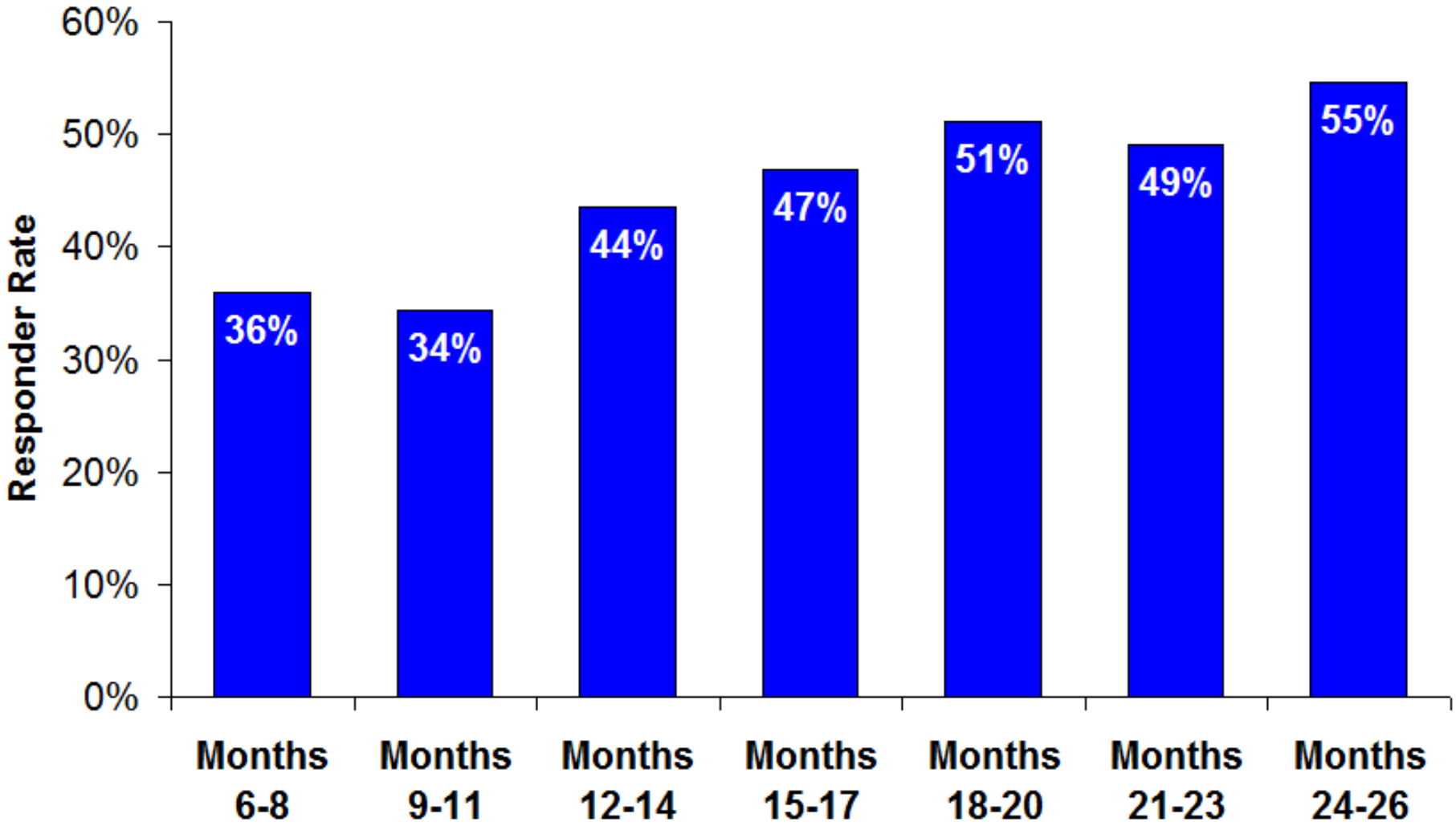
Responsive Neurostimulation (RNS)

- 191 patients
- Ages 18-70 (average age was 35)
- Refractory Partial Epilepsy
  - > 20 years duration
  - 1/3 had prior brain surgery and/or VNS

RNS

- 24 months (open label)
  - 46% responder rate
    - 7.1% seizure-free

RNS Over Time



RNS – Long Term Data

- Year 3:
  - 214 patients with 60% median seizure reduction with responder rate of 57.9%
- Year 4:
  - 204 patients with 63.3% median seizure reduction with responder rate of 60.8%
- Year 5:
  - 172 patients with 65.5% median seizure reduction with responder rate of 61%
- Year 6:
  - 115 patients with 65.7% median seizure reduction with responder rate of 59.1%

RNS – 6 Year Data

- 126 patients
- 70% median sz reduction, frontal and parietal
- 58% median sz reduction, temporal
- 26% > 6 months sz-free interval
- 14% >12 months seizure-free interval

RNS – 6 Year Data

- 111 patients MTLE
  - 66.5% median sz reduction
- 29% > 6 month sz-free interval
- 15% > 12 month sz-free interval

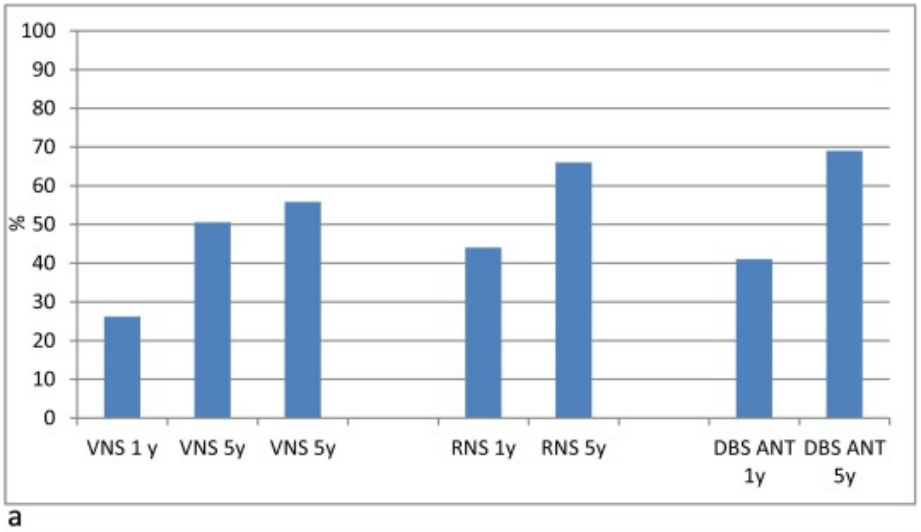
DBS in Epilepsy

- 105 patients entered the long-term follow-up phase (> 13 months)
- Median percent seizure reduction from baseline was 69% at 5 years
- 16% of the patients were seizure-free for at least 6 months
- In the study, each patient identified a most severe seizure type at the initial baseline visit
    - Median percent seizure reduction for this seizure type was 75% at 5 years

DBS Long Term by Seizure Location

- Median seizure reduction from baseline for temporal lobe seizures was 76% at 5 years
- Median seizure reduction from baseline for frontal lobe seizures was 59% at 5 years
- For patients who had previously tried VNS, median seizure reduction was 69% at 5 years
- For patients who had resective epilepsy surgery, the median seizure reduction from baseline was 67% at 5 years
- All endpoints improved compared to year one data

Five Year Results



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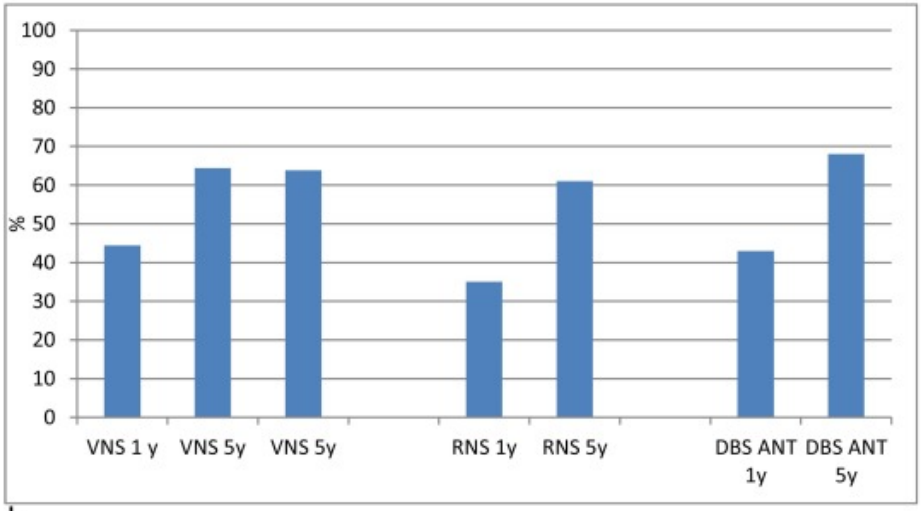

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- Top Chart is Median Seizure Reduction
- Bottom Chart is Responder Rate

- A. Schulze-Bonhage / Epilepsy & Behavior 91 (2019) 25–29

Future Treatment Gene Studies

- Ongoing antisense oligonucleotide (ASO) study in USA and abroad to decrease RNA transcription of complementary protein that worsens symptoms in Dravet
- AAV Vector study to start in 2021 to increase expression of normal SCN1a copies

Questions?


MIRACULOUS
DOC FAKERINGTON'S
GENUINE,
PURE
SNAKE OIL
1¾ FLUID OUNCES
Relieves
INSTANTANEOUSLY
HEADACHE, TOOTHACHE, BACKACHE,
EARACHE, SWELLING, INFLUENZA,
FEVER, RESTLESS SLEEP & CHEST PAIN
REMOVES WRINKLES
FOR YOUR
GLORIOUS HEALTH
ALSO POLISHES FURNISHINGS

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