Other treatments: KD & VNS

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Pharmacologic Rx
- 1st drug response - 47%
- 2nd & 3rd drug response - 14%
- Polytherapy response - 3%
- Many are intractable
- Uncontrolled by 2 drugs at proper dose


Surgical options
- Possible cure
- Not all are surgical candidates
- Surgical risk
- Limited centers
- High cost

Dietary options
- Ketogenic diet (KD)
  - LCT
  - MCT
- Modified Atkins *
- Low GI diet *
  * satisfactory preliminary result

Neuromodulations
- Vagal nerve stimulation (VNS)
- Deep brain stimulation (DBS) *
- Responsive neuro-stimulation (RNS) *
- External Trigeminal Nerve Stimulation * (eTNS)
- Transcranial magnetic stimulation * (TNS)

Ketogenic diet (KD)*
- High fat
- Low carbohydrate
- Calorie control
- Adequate protein
- Therapeutic diet for epilepsy
  As effective as an AED or VNS
Efficacy

- RCT (145 children) published in 2008
- Diet group: - 38% = 50% Sz reduction
  - 7% = 90% Sz reduction
  - 1.5% = Sz-free

Mean Sz frequency dropped by 1/3

No difference between Classical VS MCT

International guideline

- International Ketogenic Diet Study Group
- 26 ped epileptologists & dietitian (9 countries)
- Standardized protocol

Practical approach*

- Case selection
- Pre-KD assessment
- Ketosis induction
- Evaluation
- Maintenance
- KD discontinuation

Indications

- Intractable epilepsy (any age, Sz type)

Specific for

- Glucose transporter 1 (GLUT1) deficiency
- Pyruvate dehydrogenase deficiency
  - Essential energy for brain
  - Treat - seizures
    - non-epileptic symptoms
GLUT1 deficiency
- GLUT1 protein
- Transfers glucose from blood to CSF
- Low CSF glucose, normal plasma glucose
- No other cause (CNS infection/SAH)
- Intractable Sz, MR, movement disorder
- Ketone → main energy source

PDHD deficiency
- Mitochondrial dysfunction
- Lactic acidosis
- "Pyruvate-to-Acetyl CoA" defect
- Intractable Sz
- Ketone → bypass to TCA cycle

Particular benefit in*
- Tuberous sclerosis complex
- Myoclonic-astatic epilepsy
- Rett syndrome
- Dravet syndrome
- Infantile spasms
- Infants or enterally fed patients

Recent indication
- Super refractory status epilepticus
  - Status epilepticus
  - Continues or recurs
  - Despite general anesthesia Rx for 24 h
- 20 cases report (no RCT yet)

Super refractory SE
- General anaesthesia (including consideration of barbiturates), antiepileptics, drugs and full ITU support, and investigate urgency to identify cause
- No cause identified
- Cause identified
- Give IV magnesium (Severe pyridoxine in children)
- Consider sedation / tvag
- Consider neurectomy in intractable SE
- Consider hypothermia
- Consider hyperthermia
- Consider CECT, CSF drainage and other therapies, see text

Absolute Contraindication
- Long-chain 3-hydroxyacyl-CoA def
- Medium-chain 3-hydroxyacyl-CoA def
- Pyruvate carboxylase def
- Porphyria

Fatty acid transport & oxidation defect

Pre-KD evaluation*
- Counseling
- Sz assessment
- Nutritional evaluation
- Lab evaluation

Available formulas*
- Classical formula (LCT)
- MCT formula
- Modified Atkins
- Low glycemic index (LGI)

Diet route
- Bottle feed / normal food / tube feed

Classical KD
- Widely used
- 4:1 ratio of fat: protein - carbohydrate
- Main fat source = LCT
- Adequate protein > 1 g/kg
- Low carb - just to prevent hypoglycemia
- Calorie control = 75 - 100% requirement
- Fluid restriction - not necessary

Classical diet

MCT KD
- Increasingly used → better ketosis
- 30%-60% fat: total energy
- More carbohydrate allowance
- Less restrictive, bigger meal
- Similar efficacy to LCT
- MCT can’t be cooked → not palatable

MCT diet
**Examples LCT**

- 6-year old girl, BW 20 kg
  - 1400 kcal/day, 24 gm protein (1.2 g/kg/day)
  - Classic 3:1 = 135 gm fat: 46 gm prot+carb

→ 22 gm carb /day!!

**Examples MCT**

- 6-year old girl, BW 20 kg
  - 1400 kcal/day, 24 gm protein (1.2 g/kg/day)
  - MCT 50% total calories = 84 g/day
  - Protein ~ 7%, Carb ~ 15% = 53 g/day
  - LCT ~ 28% = 44 g/day
  - K:AK 1.66:1

**Sample menu: 1300 kcal, 22 g protein (MCT ~ 48% Carb ~ 10%)**

**Ketosis induction**

- Rapid induction
  - fasting (12 h - whenever ketosis)
  - admission required
  - risk of dehydration, glucose, acidosis

- diet titrating up to the target ratio

- caregiver training during admission

**Ketosis induction**

- Gradual initiation
  - without fasting
  - admission = optional
  - slower but comparable Sz control at 3 m
  - lower initial side effect

**Maintenance phase**

- Efficacy evaluation after 3 month
- Neuro
  - seizure control
  - cognitive improvement

- urine ketone - compliance
- serum ketone - Sz control

**Maintenance**
- GI & nutritional assessment
- Blood tests
- Supplements
- Oral citrate
- Adverse effects
- Sick rules

**Sick rules**

**Discontinuation**
- Diet maintenance - 2 years if effective
- longer as necessary for GLUT-1, PDHD
- Sudden glucose intake / diet cessation → Sz
- Slow weaning over 2-3 months
- overall recurrence risk - 20%
- Higher in TSC, abnormal EEG, MRI


**side effects**

Early
- Dehydration
- N/V, diarrhea
- Hyperlipidaemia
- Hyperuricaemia
- HypoCa, HypoMg
- Metabolic acidosis

Late
- Osteopenia
- Renal stones
- Low carnitine
- Fe def anemia
- Cardiomyopathy (rare)

* GI & metabolic effect
* Mostly transient

**Draw back**
- Family - Difficult recipe
- Patient - Limited meal

**Options**
- MAD
- LGIT

**Ketocalculator/Ketopaq…….+ support to help in menu planning**
Modified Atkins
- Similar composition to classical KD
- 1:1 ketogenic ratio
- Restrict carbohydrate (10-20 g/d)
- No limit on protein, fluids, and calories
- Easier meal planning
- Preliminary effective


Low GI
- Less fat than KD
- More carbohydrate 40–60 g/day
- CHO type → low glycemic index <50
- e.g. lentils, grapefruit, whole grain bread
- Less ketone level than KD
- Still preliminary effective


Neurophysiologic Stimulation

Vagal nerve stimulation
- A repetitive stimulation via left vagal nerve
- Beneficial effects on Sz
  - acute abortive effect
  - acute prophylaxis
  - long-term progressive prophylaxis
- Proven in focal & generalized & in pediatrics

VNS device
- Similar to a cardiac pacemaker
- Electrodes around left Vagal nerve
- A pulse generator in chest wall
- Stimulation parameters are programmed
- A magnet controlled by the patient → initiate stimulation
### Stimulation Parameter Setting

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>TYPICAL RANGE</th>
<th>MEDIAN SETTINGS PED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Output current</td>
<td>0.25–3.5 mA</td>
<td>1.25 mA</td>
</tr>
<tr>
<td>Signal frequency</td>
<td>20–30 Hz</td>
<td>30 Hz</td>
</tr>
<tr>
<td>Pulse width</td>
<td>250–500 µs</td>
<td>500</td>
</tr>
<tr>
<td>Signal on time</td>
<td>7–270 s</td>
<td>30 s</td>
</tr>
<tr>
<td>Signal off time</td>
<td>12 s–180 min</td>
<td>5 min</td>
</tr>
</tbody>
</table>

### Efficacy

- High was better than low stimulation
- Well tolerated in both high and low setting
- 50% Sz reduction = 30 - 50%
- Median Sz frequency reduced by 23 - 58% at 3 m, and 31 - 58% at 6 m
- Magnet activation reduced 40 -60% in duration and intensity of Sz

### Adverse effects

- Associated with implantation
  - hoarseness
  - cough
  - pain
  - paresthesia.

- Associated with stimulation
  - hoarseness
  - dyspnea

### Deep brain stimulation
Deep brain stimulation

- Disrupts regulatory feedback loops
- Closed-loop, continuous stimulation
- VNS disrupts the loops indirectly
- DBS disrupts the loops directly.

Deep brain stimulation

- Different stimulation targets being studied
- Several small studies - good efficacy
- A Large RCT in 2010 (SANTE)
  - 110 pt
  - Anterior Nucleus of the Thalamus
  - 40-60% decrease in median Sz frequency in 1 & 2 y

Responsive neuro-stimulation

- Detect & stimulate
- Subdural or depth electrode

Responsive neuro-stimulation

- Active VS sham stimulation
- Followed by open-label period

- 37.9% VS 17.3% Sz reduction (p=0.012)
- Sz reduction to 53% at 2 y
- Responder rate 38% (6m), 53% (2 y)

### Table 1. Large randomized controlled trials of brain stimulation

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Patients</th>
<th>Target</th>
<th>Seizure Frequency Reduction Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Menachem et al., 1994</td>
<td>114</td>
<td>VNS</td>
<td>27% Sham 6%</td>
</tr>
<tr>
<td>Handforth et al., 1996</td>
<td>116</td>
<td>VNS</td>
<td>29% Sham 15%</td>
</tr>
<tr>
<td>Fisher et al., 2010</td>
<td>110</td>
<td>ANT</td>
<td>40.4% Sham 14.5% (median)</td>
</tr>
<tr>
<td>Mornell et al., 2011</td>
<td>151</td>
<td>direct-seizure loci</td>
<td>37.5% Sham 17.3%</td>
</tr>
</tbody>
</table>

eTNS
eTNS
- Non-invasive
- 12 h during sleep
- An RCT in 2013
  - 50 pt → 18 wk
  - 50% Sz reduction in 40% (p=0.78)
Phase III- ongoing

Transcranial magnetic stimulation

rTMS
- brief, high-current magnetic pulse
- Low frequency decrease cortical excitability
- rapid-rate can induce a seizure

rTMS
- small non-RCT
- Only 1 small RCT
- decrease Sz frequency & interictal discharges
- Some showed controversial results
- More large, well designed studies required

Table. Trigeminal Nerve Stimulation: Major Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Control</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median change in number of seizures per month</td>
<td>-1.4</td>
<td>0.5</td>
<td>P &lt; 0.01 between groups, 18, between groups, 51</td>
</tr>
<tr>
<td>92% responder rate at 16 weeks (%)</td>
<td>65.5</td>
<td>16.8</td>
<td>P &lt; 0.01 between groups, 27/39, between groups, 0.019</td>
</tr>
<tr>
<td>92% responder rate, online treatment period (%)</td>
<td>58.2</td>
<td>21.1</td>
<td>P &lt; 0.01 between groups, 31, odds ratio, 1.73</td>
</tr>
<tr>
<td>Time to fourth seizure at baseline (d)</td>
<td>12.5</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Time to fourth seizure with treatment (d)</td>
<td>11.0</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Seizure frequency, response ratio</td>
<td>0.9</td>
<td>0.8</td>
<td>P &lt; 0.01 between groups, 0.6; between groups, 0.6</td>
</tr>
<tr>
<td>Change in Bliss Depression Inventory score</td>
<td>-0.13</td>
<td>-0.95</td>
<td>P &lt; 0.01 between groups, 0.12, odds ratio for remission, 1.6 (P = 0.002)</td>
</tr>
</tbody>
</table>

Conclusion
- KD - proven option, good efficacy
  - need good compliance
- VNS - abortive + acute prophylactic effect
  - very high cost
Investigational Rx (need further evidence)
- Mod Atkins - easy, palatable, (effective)
- RNS - (effective)
- DBS - (effective) but inconsistent implant site
- TMS, eTNS - inconsistent efficacy so far