Vagus nerve stimulation
Ketogenic diet

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Vagus nerve stimulation (VNS)

Neurostimulation therapy for epilepsy

History of VNS for epilepsy

- 1930s VNS in animal models
- 1985 First VNS Animal model of epilepsy
- 1988 EO1 Study-1st Human Implant
- 1994 European Community Approval
- 1997 5 Completed Controlled Studies (N=454)
- 1997 US and Canadian approvals (age >12 y)
- 2004 >25,000 patients (> 26 countries) treated
- 2009 >50,000 patients implanted

Mechanism

- Unclear
- Suggest interaction between subcortical structures, including the brainstem, with the neocortex.

Vagus nerve

1. Efferent outflow white matter tract for parasympathetic innervation of the organs throughout the chest and abdomen
2. Afferent component of the nerve conducts information about visceral sensation to the brainstem

: These upstream neural targets are important serotonergic and noradrenergic centers.

: This circuit is relevant not only to modulating the epileptic network, but it also impacts mood, attention, and memory

Afferent vagus nerve

- Afferent vagal A and B fibers
- Unilateral stimulation influences both cerebral hemispheres, as shown in several functional imaging studies eg. PET
- Crucial brainstem and intracranial structures have been identified including the locus ceruleus, the nucleus of the solitary tract, the thalamus, and limbic structures

Indication

VNS should be considered under these conditions:

- (1) in patients (age > 12 yo) with proven pharmacoresistant partial epilepsy that is not amenable to surgical resection (or when the patient refuses a recommendation for epilepsy surgery)
- (2) in patients with Lennox-Gastaut syndrome / symptomatic epilepsy; esp. for drop attack, tonic seizure

* There is an increasing use of VNS in children younger than 12 years old with promising result but need more long term study

Timing

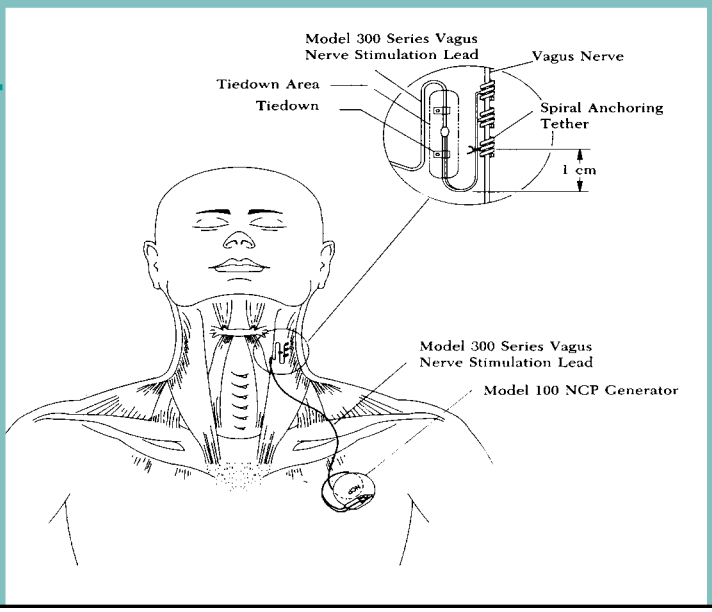
- implantation if partial seizures persist after two AED trials. Yet, there are no controlled studies to suggest that
- VNS implant may yield a better outcome than a switch to other AEDs.

VNS device

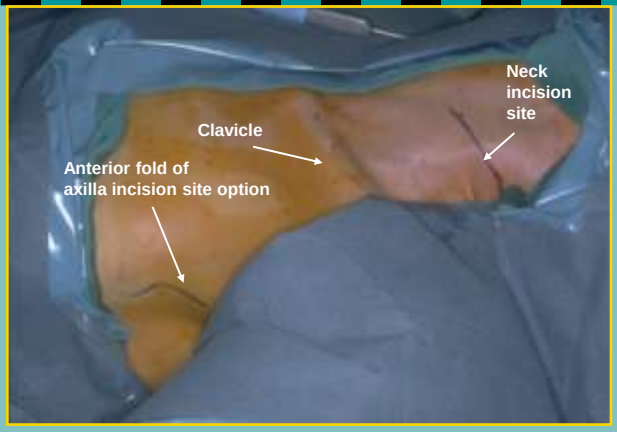
consists of a battery powered generator which is connected to a silicon polymer–coated lead wire that terminates in 3 helical contact electrodes.

Battery life: 4 years

Implantation

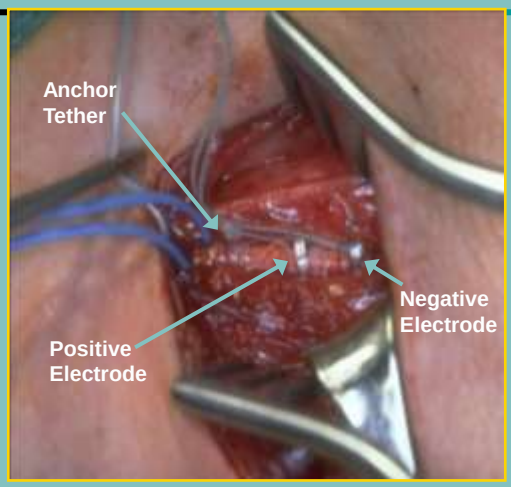


Implantation



Electrode placement

Caudal



Cephalad

VNS setting protocol

VNS is usually switched on 2 weeks after surgery.

The initial settings are:

- output current 0.25 mA
- frequency 30 Hz
- on-time 30 s, and off-time 3 min.

The output current will be increased in monthly increments of 0.25 mA to a target intensity of 1.75 mA.

The rate of increase and the maximum setting varied depending on their seizure response and the presence of side effects

Side effect

- Transient hoarseness and voice modulation associated with stimulation (55% after 12 weeks),
- Headache (22%)
- Cough, dysphagia, neck pain, shortness of breath (15-20%)

These side effects are typically parameter-related with respect to intensity, frequency, and pulse width. Each of these can be modified to minimize such effects.

- Infection (5-7%)
- Vocal cord paralysis: rare (1%)

Outcome

- Overall, 30 to 40% of individuals implanted have had at least a 50% reduction in seizure frequency in long term study (> 5 years F/U)
- Seizure freedom has been reported in only 5% of patients.
- Also improve quality of life, mood, attention, and learning

VNS: SUMMARY

- VNS can have antiepileptic effects; the mechanism is unknown
- VNS has a different spectrum of adverse events compared to drug therapy
- VNS is a safe and effective epilepsy treatment based on a preponderance of Class I evidence in adults (only Class III evidence in children)
- It is a reasonable treatment option in patients with intractable epilepsy who are not candidates for surgical or dietary treatment

Ketogenic diet (KD)

In the Beginning…

- In the 5th Century BC, Hippocrates reported that complete abstinence from food and drink was effective in treating epilepsy.

The Early 20th Century

- 1911 - Guelpa and Marie reported on the efficacy of fasting in the treatment of epilepsy
- 1921 - Wilder proposed an actual diet that mimicked biochemical changes seen in fasting
- 1938 - after nearly 20 yrs of widespread use of the KD in the treatment of epilepsy in children (and some adults), new anticonvulsants were produced and use of the KD waned for many decades.

Ketogenic Revival

- Early 1990s - a 2 yr old with intractable epilepsy was successfully treated with the KD at Johns Hopkins Hospital

The ketogenic diet: What?

- The KD is a low carbohydrate, high fat, and adequate protein diet
- Mimics the body's state of starvation
- Ketones, not glucose, become the primary source of fuel for the brain
- Calculations based on age, sex, height, weight and activity/stress factors

Fat and ketone

Fat is metabolized by liver →

- 1) acetoacetate
- 2) beta-hydroxybutyrate
- 3) acetone

- 1) + 2) = keto acids
- 3) = true ketone
- 1) + 2) + 3) = ketone bodies

Mechanism: hypothesis?

- pH Hypothesis: Acidosis in blood and brain may stop Sz?
- Metabolic Hypothesis?
  : Increased brain energy; ketone body produces more ATP than glucose
  : Increased mitochondrial number; more energy for brain?
  : Fast energy (glucose from glycolysis); Sz need fast energy. ketone provide slow energy (Krebs cycle)
- Amino acid Hypothesis: KD modify balance of neurotransmitter (GABA)?
- Ketone Hypothesis: ketone bodies or acetone have direct anticonvulsant effects on the brain?

Indication

- Children with epilepsy that is not controlled with medication
- Willing to commit the time and effort required (family and child) and understand potential risks/complications
- Resective epilepsy surgery is not an option

KD has been reported to be helpful

- Probable
  - GLUT-1 def. glocose transporter 1 def.
  - PHD: Pyruvase dehydrogenase deficiency
  - Doose syndrome: Myoclonic-astatic epilepsy
  - Tuberous Sclerosis Complex, Rett syndrome
  - Severe myoclonic epilepsy of infancy (Dravet syndrome)
  - Infantile spasms

Kossoff et al. Epilepsia, 2008

Suggestion of benefit with KD

- Selected mitochondrial disorders
- Glycogenosis type V
- Landau-Kleffner syndrome
- Lafora body disease
- Subacute sclerosing panencephalitis

Kossoff et al. Epilepsia, 2008

Contraindications to use of KD

- Absolute
  - Carnitine def. or CPT I or II def., Carnitine tranlocase deficiency
  - B-oxidation defects (MCAD, LCAD, SCAD)
  - Pyruvate carboxylase deficiency
  - Porphyria
- Relative
  - Inability to maintain adequate nutrition, caregiver noncompliance, surgical candidate
  - High cholestrol, bone disease

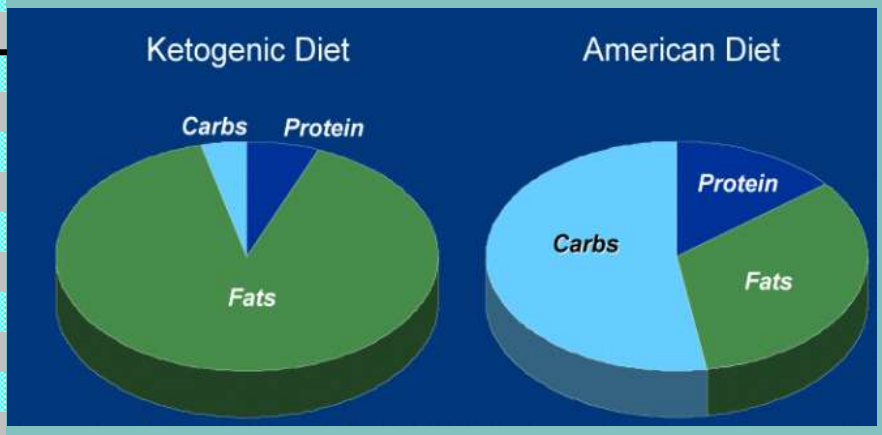
Kossoff et al. Epilepsia, 2008

Dietary therapies for epilepsy

- **Classic ketogenic diet**
- Medium chain triglyceride ketogenic diet
- Modified Atkins diet
- Low glycemic index diet

Classic Ketogenic Diet

- Classic KD is a diet made up of specific ratios of fat to protein and carbohydrates
- Ratio typically ranges from 2:1 (e.g. 2 parts fat to 1 part protein + carbohydrates) to 4:1



Healthy Diet vs. KD

Diet Content	Typical Diet	Classic KD
Carb.	55%	3%
Protein	15%	7%
Fat	30%	90%

Classic KD Food Groups

- Whipping cream
- Butter / oil
- Vegetables and/or fruit
- Protein

Starting the diets

- Hospital admission
- Skip breakfast, start with shakes
- Increase diet ratio or MCT %
- Caregiver teaching
- Monitor for adverse effects

Ketone and Blood sugar monitoring

- Urine ketones aid with tailoring diet to each child
- Blood sugars routine at diet onset, later as needed

Supplementation

- Universal Recommendations
  - Multivatimins with minerals (and trace minerals)
  - Calcium with Vitamin D
- Optional Extra Supplementation
  - Oral citrates (Polycitra K)
  - Laxatives (Miralax, mineral oil, glycerin suppository)
  - Additional selenium, magnesium, zinc, phosphorus, vitamin D
  - Carnitine
  - MCT oil or coconut oid (source of MCT)
  - Salt (sodium to add to modular formulas if used for greater than age 1 year)

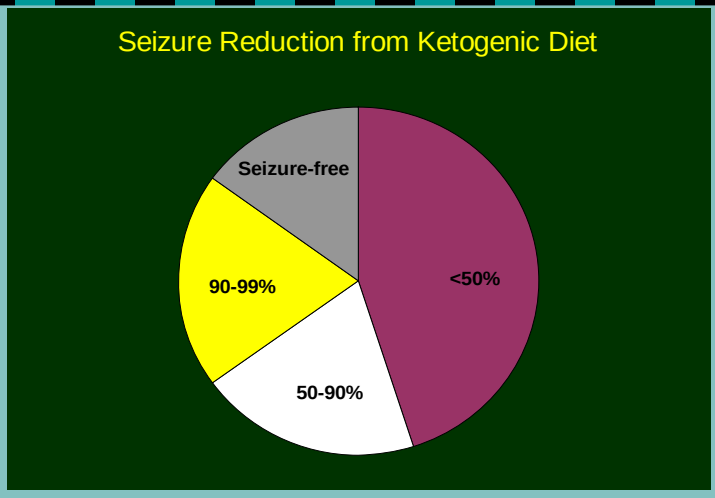
All supplements should be provided as CHO-free preparations whenever possible

Kossoff, et al.

Short-term benefit

- KD works quickly when effective, typically within the first 1–2 weeks
- It has been reported that fasting, even before actual ketogenic food is provided, can lead to a rapid improvement in seizures.
- Median time at which parents reported significant seizure reduction was after 5 days (range, 1–65 days) from 99 patients who response to KD
- If the KD has not led to seizure reduction after 2 months, it can probably be discontinued

Effectiveness at 3-6 month F/U



Long-term benefit

- Neuroprotection: seizure reduction may be seen long term even when the diet is discontinued after only a few months of use
- Antiepileptogenic effect: in animal study

Pharmacodynamic interactions between KD and AEDs

- No combination that yields greater or less efficacy
- Serum levels do not appear to be altered by KD (Dahlin, 2006;Ped Neurol 35: 6-10)
- Recent evidence supports safe use of VPA and KD (Lyczkowski, 2005;Epilepsia 46: 1533-8)
- Secondary carnitine deficiency which can occur with either the KD or VPA alone can be worsened (Coppola,2006; Brain Dev. 358: 358-365)

Dietary Therapy Complications

- Acute:
  - Acidosis
  - Dehydration
- Chronic
  - Elevated cholesterol/triglycerides
  - Constipation/diarrhea
  - Kidney stones
  - Poor linear growth
  - Nutritional deficiency
  - Immune deficiency?

Teach Parents to read labels & find CHO information

- Never assume a food is low in carbs – always read the food label or check the carb counter
- Look for hidden carbs in gravies, sauces, prepared salads, salad dressing and other dressings, which are often made with flour, cornstarch or sugar
- Sugar free, sugar-less and no sugar added does not mean low carb
- Many products which we do not think of as food (mints, cough drops,) have sugar
- Medications, especially liquids, syrups, suspensions and chewable tablets, often contain carbohydrate – check with pharmacist or medical team
- GUM also has sugar

What happens if a child on KD needs in-patient hospitalization?

- Ensure medications are carbohydrate free
  - All oral medications must be in TABLET form.
  - Suspensions, syrups and chewable tables have excess carbohydrates. Sugar free liquid medications are not permitted as they may contain carbohydrates. When in doubt, discuss with a pharmacist
- No IV Dextrose solutions unless absolutely necessary.
- Ask the caregiver about patient's ketogenic diet regimen.
  - Families have been instructed to bring their child's diet orders and menus to the hospital. Diet regimens include required daily fluid intake.
  - Need to work closely with dietician while in hospital

Caring for child on KD in hospital

- Check urine ketones with every void, at least twice per day.
  - If the urine ketone level is >16 mmol/L or child is symptomatic of hyperketosis, treat immediately with 15 ml of orange juice or 10 ml of apple juice.
- Measure urine specific gravity with each void.
  - Urine specific gravity should be <1.035.
  - If urine specific gravity is >1.035, increase fluid intake to ensure hydration.
  - Confirm the prescribed maximum daily fluid intake.

Hospitalized child on KD: Check blood glucose

- **At least every 6 hours for ill patients.**
- **Twice daily for stable patients, prior to breakfast and dinner or first and last G-tube feed.**
  - Glucose is < 2.5 mmol/L or if symptomatic for hypoglycemia, treat immediately with 30 mL of orange juice or 20 mL of apple juice. Recheck within 1 hour. If remains < 2.5 mmol/L, treat immediately with 15 ml of orange juice or 10 ml of apple juice.
  - Glucose is between 2.5-3.0 mmol/L, treat immediately with 15 ml of orange juice or 10 ml of apple juice. Recheck in 1 hour.

Conclusions

- Diet treatment can be successful in controlling seizures in children with intractable epilepsy
- New diets are being developed with improved palatability and ? fewer side effects