



## ALTERNATIVE TREATMENT OPTIONS FOR DRAVET SYNDROME: HIGH-FAT DIETS AND VAGUS NERVE STIMULATOR (VNS)

## ALTERNATIVES AUX ANTICONVULSANTS DANS LE TRAITEMENT DE L'ÉPILEPSIE CHEZ LE PATIENT AVEC SYNDROME DE DRAVET: LES DIÈTES CÉTOGÈNES ET LE STIMULATEUR DU NERF VAGUE.

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# Introduction

- ▶ Epilepsy in children with Dravet syndrome is often difficult to control with medications.
  - ▶ Drug-resistant epilepsy: failure of 2 appropriate anticonvulsants after adequate and tolerated trials
- ▶ These children, as well as hundreds thousands adults, need alternative treatments to anticonvulsant medications.
- ▶ L'épilepsie chez les enfants atteints du syndrome de Dravet est souvent difficile à contrôler avec les médicaments.
  - ▶ Épilepsie réfractaire: absence du contrôle des crises malgré l'essais de deux anticonvulsivants appropriés
- ▶ Ces enfants, ainsi que des centaines de milliers d'adultes, ont besoin d'alternatives aux anticonvulsivants pour le traitement de l'épilepsie

# Plan

- ▶ Vagus Nerve Stimulator
- ▶ High-fat diets
- ▶ Stimulateur du Nerf Vague
- ▶ Diètes hautes en gras



# Vagus nerve stimulator

# Stimulateur du nerf vague

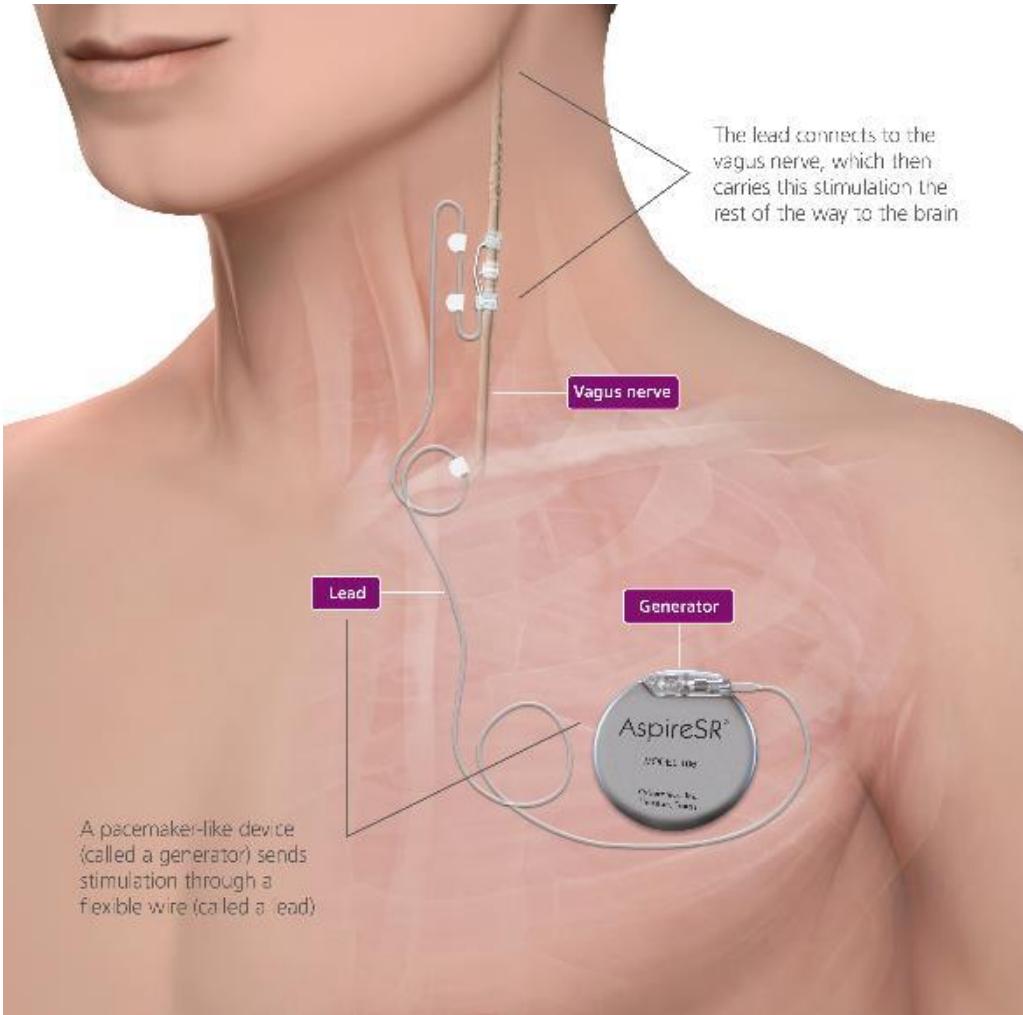
# Introduction

- ▶ First human implanted in 1988 (Penry et al.)
- ▶ Mechanism of action
  - ▶ Not well understood
- ▶ Possible benefits
  - ▶ Reduced seizure frequency
  - ▶ Reduced seizure severity
  - ▶ Termination of seizures through use of external VNS magnet
  - ▶ Decreased ER visits
  - ▶ Diminished antiepileptic drug requirement
  - ▶ Improvement in quality of life
- ▶ Premier VNS implanté chez l'humain en 1988 (Penry et al.)
- ▶ Mécanisme d'action
  - ▶ Peu compris
- ▶ Bénéfices possibles
  - ▶ Diminution de la fréquence des crises
  - ▶ Diminution de la sévérité des crises
  - ▶ Arrêt des crises avec l'utilisation de l'aimant
  - ▶ Diminution des visites à l'urgence
  - ▶ Diminution de nombre d'anticonvulsivants
  - ▶ Amélioration de la qualité de vie

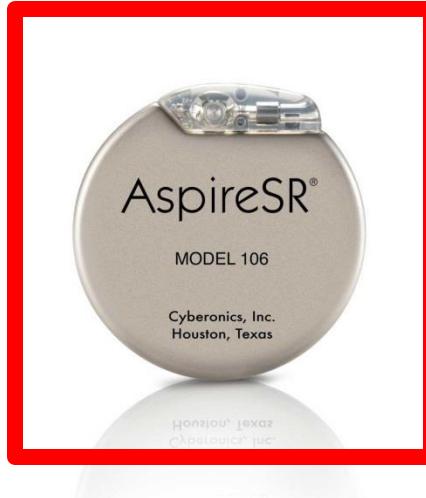
# Indications

- ▶ Patients with drug-resistant epilepsy not suitable for resective surgery
  - ▶ Resective surgery preferred in good candidates
- ▶ Patients avec épilepsie réfractaire qui ne sont pas candidats à une chirurgie résective
  - ▶ Chirurgie résective préférée chez les bons candidats

# System and hardware



# System and hardware



Pulse Model 102	6.9 mm x 52.2 mm x 51.6 mm
Pulse Duo Model 102R	6.9 mm x 58.9 mm x 51.6 mm
Demipulse Model 103	6.9 mm x 45.0 mm x 32.0 mm
Demipulse Duo Model 104	6.9 mm x 45.0 mm x 39.0 mm
AspireHC Model 105	6.9 mm x 52.0 mm x 52.0 mm
Lead Model 303 & 304	2.0 & 3.0 mm



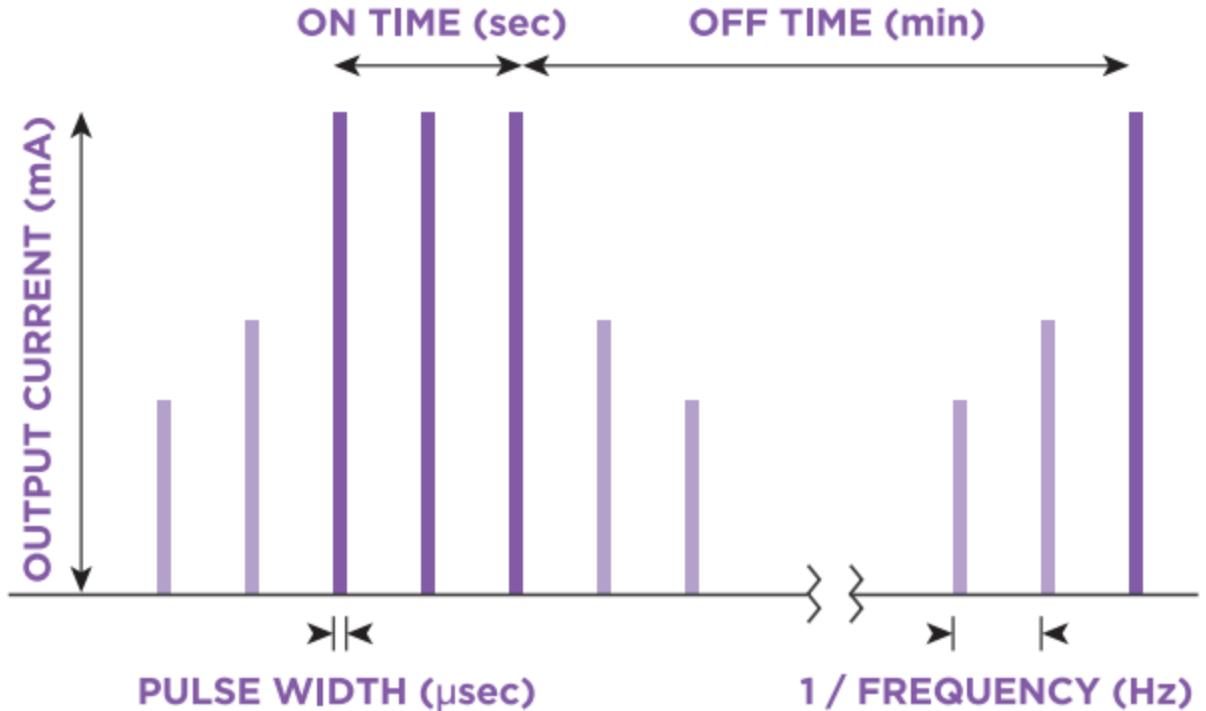
303



304

# Programming

## NORMAL MODE

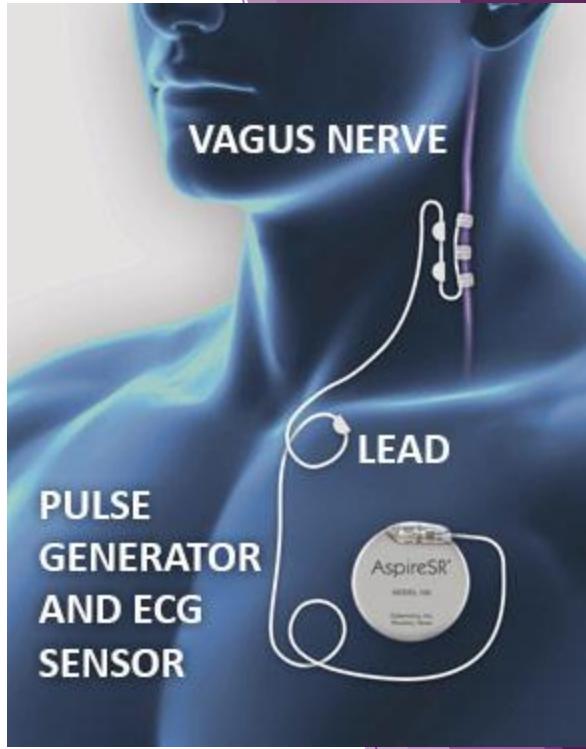
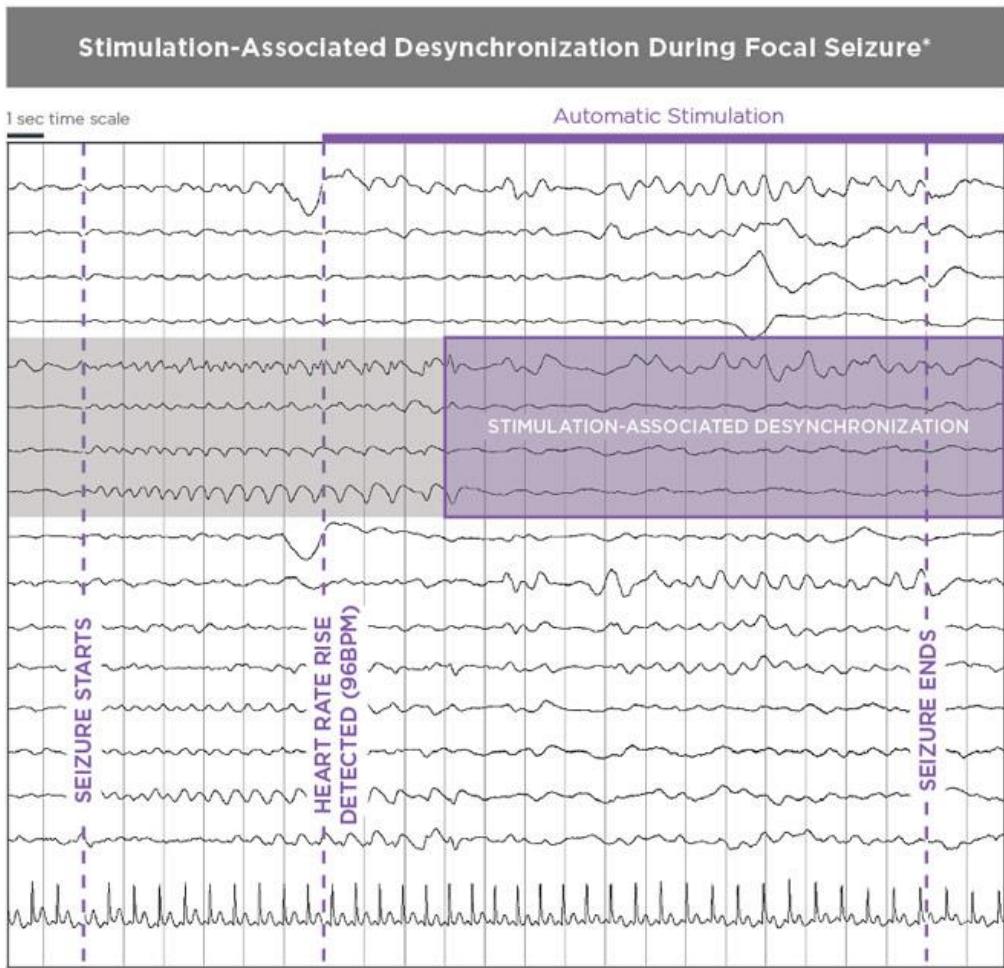


MAGNET MODE: with magnet activation

AUTOSTIM MODE (AspireSR 106): automatic seizure detection



# Autostimulation mode (AspireSR 106)



# Programming

## Phase 1: Output Current

Increase Output Current to therapeutic range as quickly as tolerable

### NORMAL MODE



### THERAPEUTIC RANGE <sup>1,2</sup>

**MAGNET MODE:** Normal Mode + 0.25 mA

*Magnet Mode must be > than AutoStim Mode\**

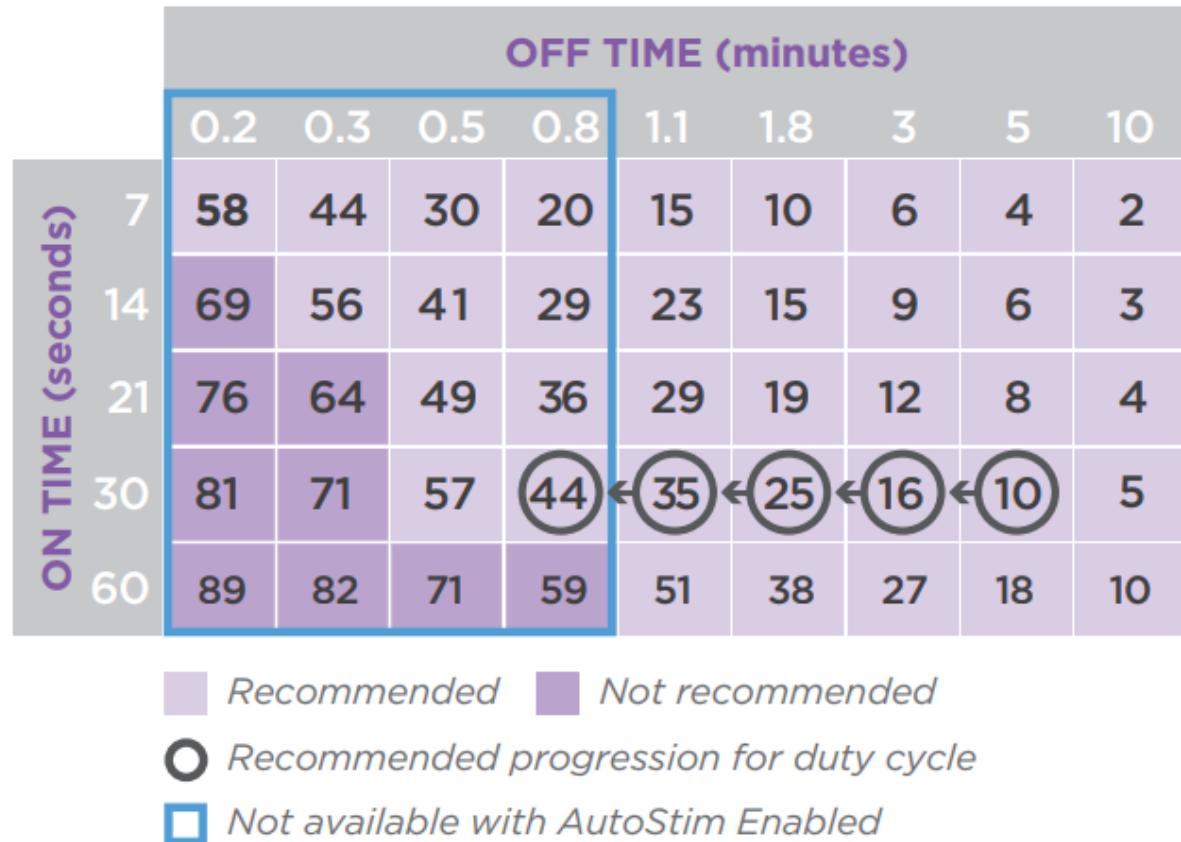
**AUTOSTIM MODE†:** Normal Mode + 0.125 mA

*AutoStim should be comfortable for patients*

# Programming

## Phase 2: Duty Cycle

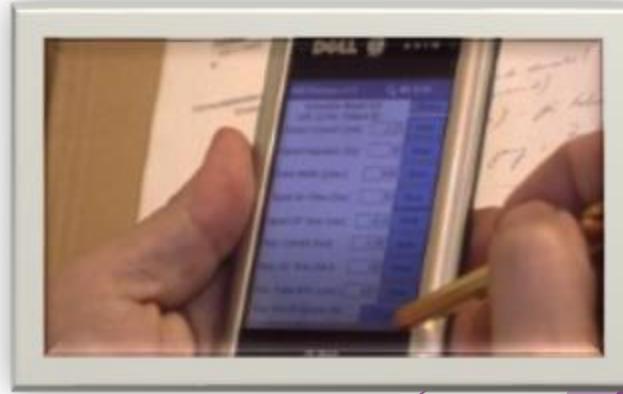
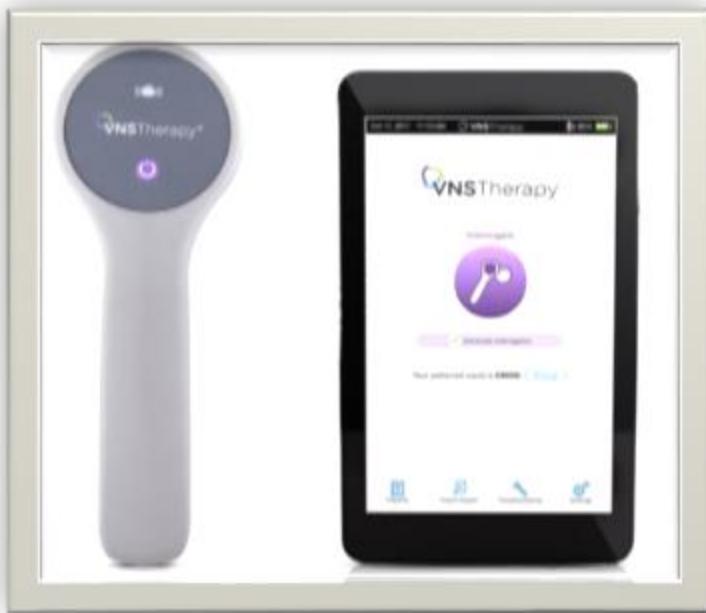
Increase duty cycle over time and assess clinical outcome



## Suggested Initial Programming Settings ( $\geq$ 2 Weeks Post-Op)

NORMAL	Output Current	0.25 mA	
	Frequency	30 Hz	
	Pulse Width	500 $\mu$ sec	
	<b>DUTY CYCLE: 10%</b>		
	ON Time	30 sec	
	OFF Time	5 min	
MAGNET	Output Current	0.5 mA	
	ON Time	60 sec	
	Pulse Width	500 $\mu$ sec	
AUTOSTIM <sup>†</sup>	Output Current	0.375 mA	
	ON Time	60 sec	
	Pulse Width	500 $\mu$ sec	

# Interrogation and programming



# Efficacy

## Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response

A review

DARIO J. ENGLOT, M.D., PH.D., EDWARD F. CHANG, M.D., AND KURTIS I. AUGUSTE, M.D.

TABLE 1: Summary of Class I, II, and III evidence of VNS efficacy in treating epilepsy\*

Study	No. of Cases	Seizure Type	Notes	Follow-Up	No. of Centers	Median or Mean % Seizure Reduction	% Patients w/ >50% Reduction†
<b>Class I evidence</b>							
Ben-Menachem et al., 1994	114	partial	high vs low stim comparison	3 mos	multi	25 vs 6	31
Handforth et al., 1998	196	partial	high vs low stim comparison	3 mos	multi	28 vs 15	23
Amar et al., 1998	17	partial	high vs low stim comparison	3 mos	single	71 vs 6	57
<b>Class II evidence</b>							
Scherrmann et al., 2001	28	mixed	2 stim paradigms	NR	single	30 overall	45
DeGiorgio et al., 2005	61	partial	3 stim paradigms	3 mos	multi	26 overall	29
<b>Class III evidence</b>							
Ben-Manachem et al., 1999	64	mixed		3–64 mos	single	NR	45
Parker et al., 1999	15	mixed	children w/ encephalopathy	1 yr	single	17	27
Labar et al., 1999	24	gen		3 mos	single	46	46
DeGiorgio et al., 2000	195	mixed		12 mos	multi	45	35
Chavel et al., 2003	29	partial		1–2 yrs	single	53	54‡
Vonck & colleagues, 1999 & 2004	118	mixed		>6 mos	multi	55	50
Majoie & colleagues, 2001 & 2005	19	mixed	children w/ encephalopathy	2 yrs	single	20.6	21
Huf et al., 2005	40	NR	adults w/ low IQ	2 yrs	single	26	28
Kang et al., 2006	16	mixed	children	>1 yr	multi	50	50
Ardesch et al., 2007	19	partial		>2 yrs	single	25§	33§

21–57%

# Efficacy | Efficacité

- ▶ Results Meta-Analysis
  - ▶ 3341 patients
  - ▶ % Reduction in seizure frequency at last follow-up compared to baseline
  - ▶ % Réduction de la fréquence des crises au dernier follow-up comparativement à avant le VNS
    - ▶ Mean | Moyenne: 44.6% +/- 0.5%
    - ▶ Impact of treatment duration | Impact de la durée depuis l'implantation?
      - ▶ 3-12 months after surgery: 36.2 +/- 0.5%
      - ▶ > 1 year after surgery: 51.0 +/- 0.5%

Suggests delayed benefit to sustained VNS therapy  
Suggère une réponse maximale après ≥1 an

TABLE 2: Seizure outcomes reported by Engel class

Parameter	Engel Class, % Seizure Decrease				Total*
	I, 100%	II, >90%	III, 50%-90%	IV, <50%	
no. of patients (%)	121 (4.6)	200 (7.6)	1012 (38.4)	1301 (49.4)	2634

\* Only individuals for whom Engel classification could be determined are tallied.

Engel I-III ( $\geq 50\%$  reduction): 50.6%  
Engel I-II ( $\geq 90\%$  reduction): 12.2%

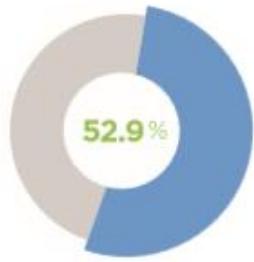
# Efficacy of adjunctive vagus nerve stimulation in patients with Dravet syndrome: A meta-analysis of 68 patients

Maxine Dibué-Adjei<sup>a,\*</sup>, Igor Fischer<sup>b</sup>, Hans-Jakob Steiger<sup>b</sup>, Marcel Alexander Kamp<sup>b</sup>

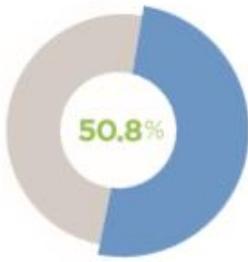
<sup>a</sup> LivaNova Deutschland GmbH, LivaNova PLC-owned subsidiary, Lindberghstr 25, 80939 Munich, Germany

<sup>b</sup> Department of Neurosurgery, Medical Faculty, Heinrich-Heine-University, Moorenstraße 5, D-40225 Düsseldorf, Germany

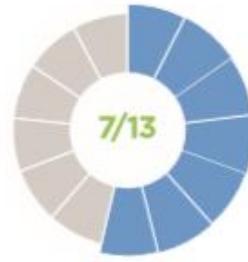
**Meta-Analysis of 13 studies** including 68 Patients with Dravet Syndrome  
treated with VNS Therapy<sup>10</sup>



Responder Rate \*  
(N=68)



Mean Seizure Reduction  
(N=28)

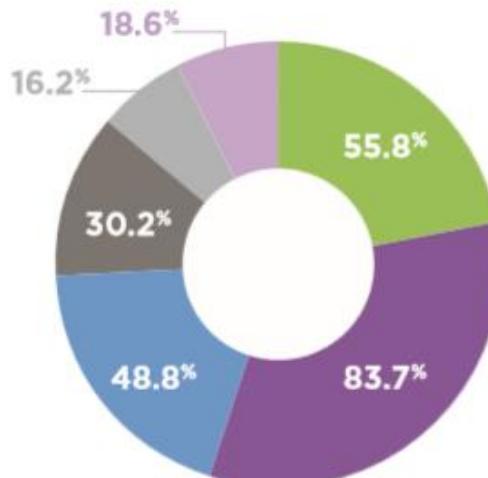


Studies Reported Benefits  
beyond Seizure  
Frequency Reduction

## Self-reported outcomes from care-givers and parents of patients with Dravet Syndrome

Percentage of care-givers and parents of patients with Dravet Syndrome reporting beneficial changes after VNS Therapy<sup>11</sup>

- seizure frequency
- improvement in seizure severity
- reduced hospital admissions
- improved cognition
- improved ability to participate in school work
- improved emotional interaction



\* >50% reduction in frequency of overall seizures or predominant seizure type

TABLE 3: Incidence of adverse effects of VNS for epilepsy

Parameter	Ben-Menachem et al., 1994	Handforth et al., 1998	DeGiorgio et al., 2000
no. of patients	114	196	195
follow-up (mos)	3	3	12
adverse effect (% cases)			
hoarseness	37	62	55
cough	7	21	15
paresthesia	6	25	15
pain	6	17	15
dyspnea	6	16	13
headache	2	20	16
infection	NR	4	6

# Tolerability

## ► Side effects

- ▶ Surgical risks and infections
- ▶ Usually during stimulation
  - ▶ Most common
    - ▶ Hoarseness, voice change | Voix rauque
    - ▶ Coughing | Toux
    - ▶ Abnormal throat sensation | Sensation anormale gorge
    - ▶ Difficulty breathing (dyspnea) | Difficultés respiration (dyspnée)
    - ▶ Drooling | Augmentation salive
    - ▶ Difficulty swallowing (dysphagia) | Difficultés à avaler (dysphagie)
      - ▶ More common if previous history of dysphagia
    - ▶ Erosion of the skin (decreased with implantation under pectoralis) | Érosion peau
    - ▶ Etc.
- ▶ Device malfunction (e.g. lead fracture)

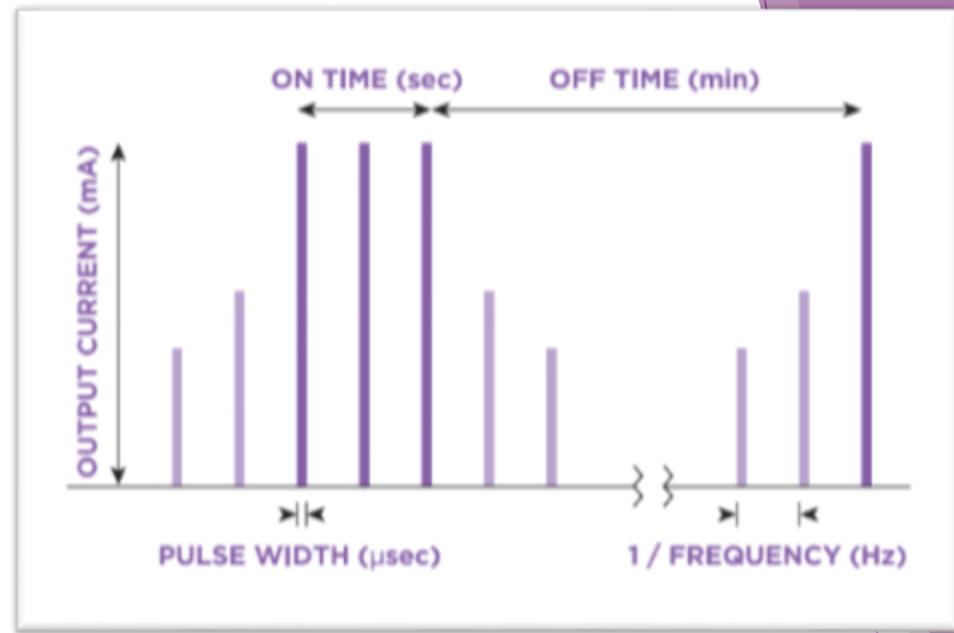
J Neurosurg 115:1248–1255, 2011

Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response

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# Tolerability



## Strategies to Manage Side Effects

- Evaluate tolerability after each adjustment
- Side effects typically decrease over time<sup>3,4</sup>

RECOMMENDED ORDER	
1. Pulse Width	500 → 250 $\mu$ sec
2. Signal Frequency	30 → 25 or 20 Hz
3. Output Current	↓ 0.125 mA (AspireSR) ↓ 0.25 mA

# System and hardware

- ▶ Battery life | Durée de vie de la batterie
  - ▶ New devices
    - ▶ Low stimulation: 10-12 years
    - ▶ High stimulation: 5 years
  - ▶ Old devices
    - ▶ Shorter
- ▶ Brain MRI | MRI tête
  - ▶ Considered safe with VNS | Sécuritaire avec le VNS
    - ▶ 1.5 and 3T magnet
    - ▶ Output current set to “0” before and reprogrammed after MRI
    - ▶ Device interrogated after MRI
- ▶ According to the manufacturer, the following should NOT affect the pulse generator | Aucun risque avec:
  - ▶ Microwave
  - ▶ Ovens
  - ▶ Toasters
  - ▶ Hair dryers
  - ▶ Electrical appliances
  - ▶ Cellular phones
  - ▶ Metal detectors at the airport



# High-fat diets

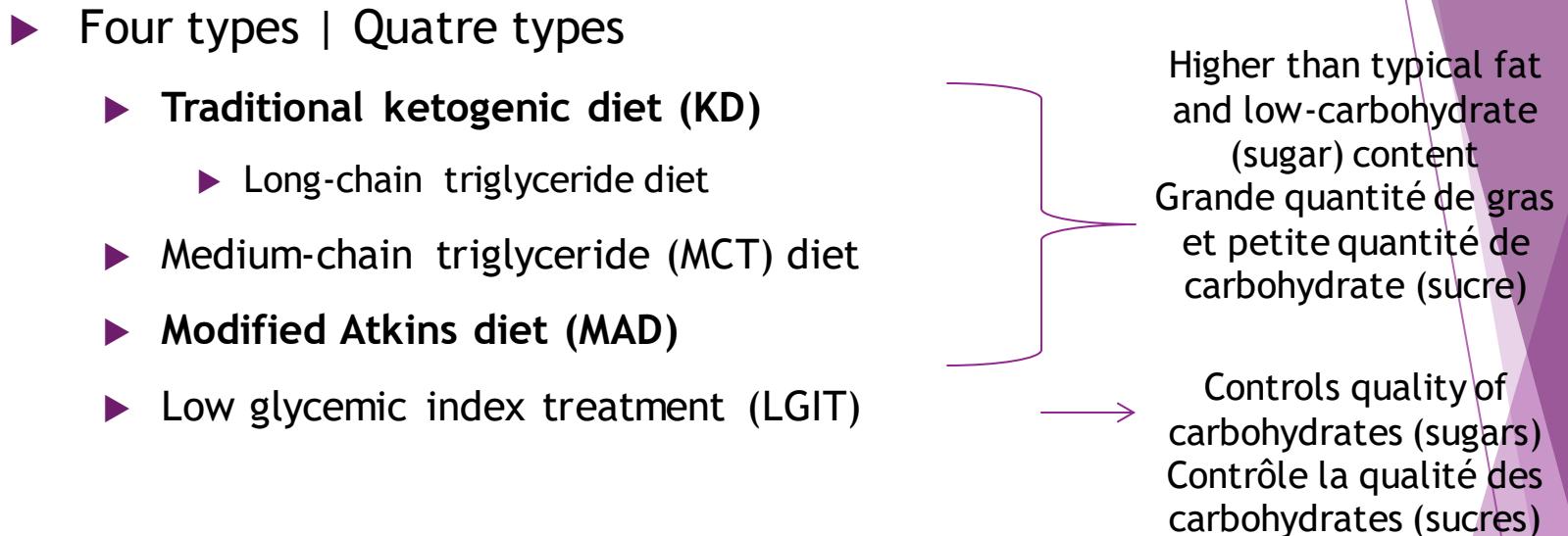
# Diètes hautes en gras

# High-fat diets

- ▶ Centuries ago, Hippocrates was the first to note that fasting treated convulsions.
- ▶ Concept rediscovered in the early 20<sup>th</sup> century by Guelpa and Marie in 1911
  - ▶ Ketogenic diet developed in 1920 at the Mayo Clinic by Wilder
  - ▶ Designed to mimic the beneficial effects of fasting
    - ▶ Restriction of carbohydrates, protein and fluids
    - ▶ Increase fat intake to 90% of total calories
  - ▶ Widely used for adults and children with epilepsy for the next 20 years
- ▶ Less used with the introduction of “newer” anticonvulsants
- ▶ The story of Charlie Abrahams
  - ▶ 20-month-old boy from California with medically and surgically refractory epilepsy
  - ▶ Became seizure free within days of initiation of the traditional ketogenic diet (Johns Hopkins Hospital)
  - ▶ **Charlie Foundation** created in 1994 to promote research, awareness and availability of the ketogenic diet.

Ketogenic diet now available in over **50 countries**, in all continents except Antarctica

# Metabolic treatments

- ▶ Four types | Quatre types
    - ▶ Traditional ketogenic diet (KD)
      - ▶ Long-chain triglyceride diet
    - ▶ Medium-chain triglyceride (MCT) diet
    - ▶ Modified Atkins diet (MAD)
    - ▶ Low glycemic index treatment (LGIT)
- 
- Higher than typical fat and low-carbohydrate (sugar) content  
Grande quantité de gras et petite quantité de carbohydrate (sucre)
- Controls quality of carbohydrates (sugars)  
Contrôle la qualité des carbohydrates (sucres)

## SPECIAL REPORT

# Indications

### Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group

- ▶ Drug-resistant epilepsy | Épilepsie réfractaire
  - ▶ Focal and generalized seizures | Crises focales et généralisées
- ▶ Resective surgery preferred in good candidates | Chirurgie résective préférée chez les bons candidats

**Table 1. Epilepsy syndromes and conditions in which the KD has been reported as particularly beneficial**

Probable benefit (at least two publications)
Glucose transporter protein I (GLUT-I) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Myoclonic-astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Infantile spasms
Children receiving only formula (infants or enterally fed patients)
Suggestion of benefit (one case report or series)
Selected mitochondrial disorders
Glycogenosis type V
Landau-Kleffner syndrome
Lafora body disease
Subacute sclerosing panencephalitis (SSPE)

**Table 2. Contraindications to the use of the KD**

Absolute
Carnitine deficiency (primary)
Carnitine palmitoyltransferase (CPT) I or II deficiency
Carnitine translocase deficiency
$\beta$ -oxidation defects
Medium-chain acyl dehydrogenase deficiency (MCAD)
Long-chain acyl dehydrogenase deficiency (LCAD)
Short-chain acyl dehydrogenase deficiency (SCAD)
Long-chain 3-hydroxyacyl-CoA deficiency
Medium-chain 3-hydroxyacyl-CoA deficiency.
Pyruvate carboxylase deficiency
Porphyria
Relative
Inability to maintain adequate nutrition
Surgical focus identified by neuroimaging and video EEG monitoring
Parent or caregiver noncompliance

# Ketogenic diet: in summary

- ▶ Hallmark feature is ketosis via increased metabolism of fat
  - ▶ Sugar (carbohydrate) severely restricted
  - ▶ Exogenous fat sources
    - ▶ Fat provides the majority of calories
    - ▶ Induces combustion of fats for fuel
    - ▶ Ketones are the product of fat metabolism
  - ▶ Protein based on minimum daily requirement
  - ▶ Adequate fluid intake
    - ▶ Helps prevent constipation and kidney stones
  - ▶ Calories not restricted
- ▶ Base de la diète est la production des corps cétoniques via le métabolisme des gras
  - ▶ Sucre (carbohydrate) sévèrement limité
  - ▶ Beaucoup de gras dans l'alimentation
    - ▶ Les gras constituent la majorité des calories
    - ▶ Les corps cétoniques sont produits par le métabolisme des gras et sont utilisés comme source d'énergie
  - ▶ Protéines: minimum requis pour croissance
  - ▶ Apport de liquides adéquat
    - ▶ Diminue les risques de pierres aux reins et diminue la constipation
  - ▶ Pas de restriction des calories

# Ketogenic diet: in summary

## ► Ratio

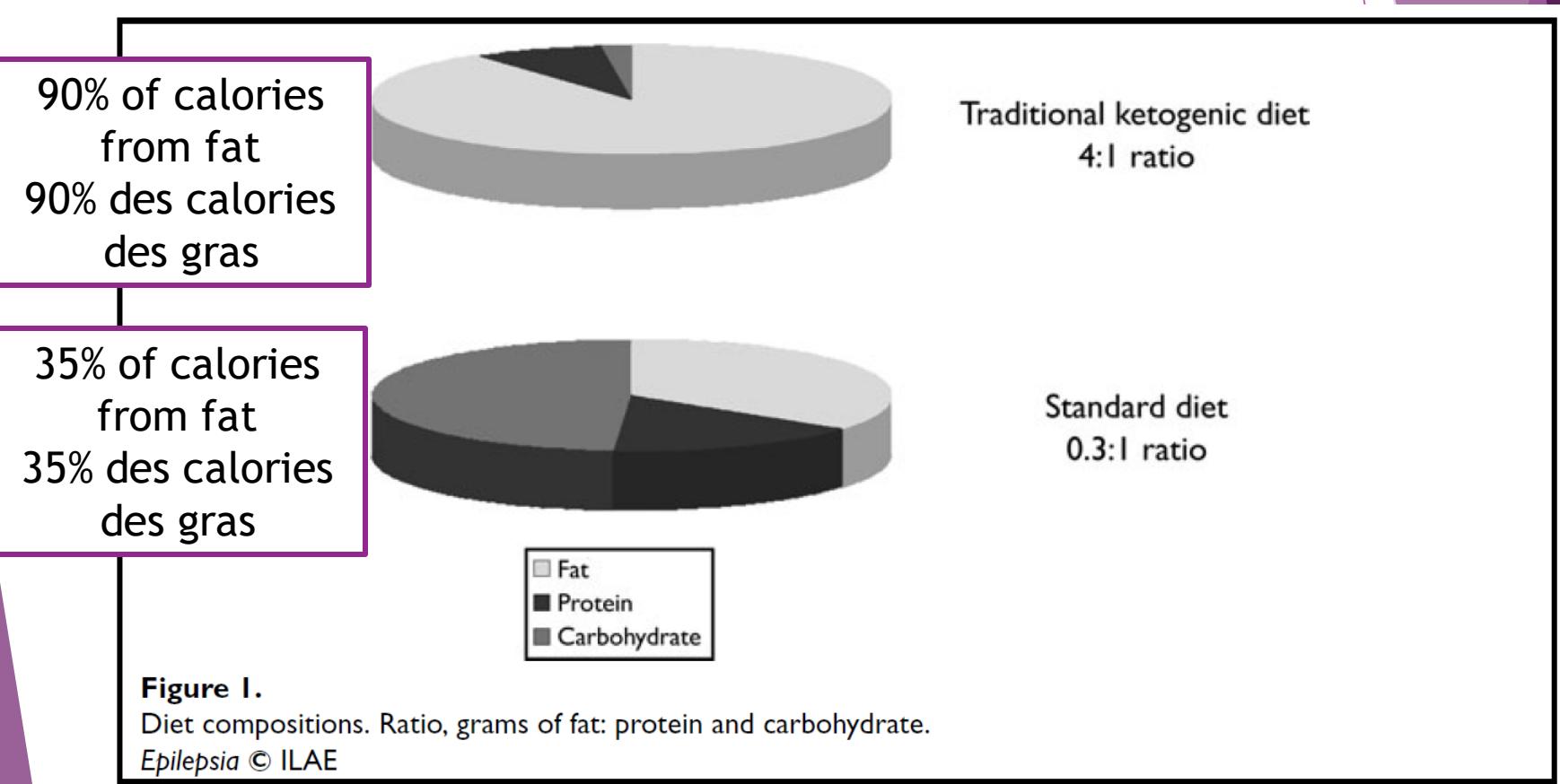
- ▶ Grams of **fat** : grams of **protein + sugar (carbohydrate)**
- ▶ Typical ratio:
  - ▶ 4:1 ratio
  - ▶ 3:1 ratio

## ► Ratio

- ▶ Grammes de **gras**: grammes de **protéines + sucre (carbohydrate)**
- ▶ Ratios typiques:
  - ▶ 4:1
  - ▶ 3:1

# Traditional ketogenic diet

- ▶ What about a regular diet?



# Traditional ketogenic diet

- ▶ 4:1 Ratio Meal
  - ▶ Scrambled eggs, bacon, cantaloupe, cream



Courtesy of Aaron Owens, MS, RD, CSP,  
And Marta Mazzanti, MS, RD, CD

# Traditional ketogenic diet

- ▶ 4:1 Ratio Meal
  - ▶ Hot dog, salad with mayonnaise, carrot curls, frozen cream, sugar-free Jell-O



Courtesy of Aaron Owens, MS, RD, CSP,  
And Marta Mazzanti, MS, RD, CD



# Modified Atkins diet

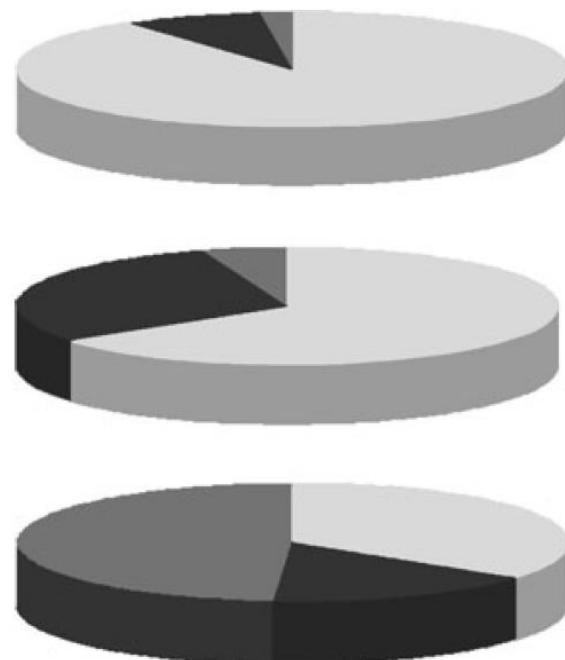
- ▶ First described in 2003 (Johns Hopkins)
- ▶ **Sugar (carbohydrates) limited to 10-20g per day**
- ▶ **Fats strongly encouraged**
- ▶ Foods are not weighed and measured
- ▶ Développée en 2003 (John Hopkins)
- ▶ Limitation des sucres (carbohydrates) à 10-20g par jour
- ▶ Gras fortement encouragés
- ▶ Nourriture n'est pas pesée ou mesurée

# Modified Atkins diet

90% of calories  
from fat  
90% des calories  
des gras

70% of calories  
from fat  
70% des calories  
des gras

35% of calories  
from fat  
35% des calories  
des gras



Traditional ketogenic diet  
4:1 ratio

Modified Atkins diet  
1:1 ratio

Standard diet  
0.3:1 ratio

**Figure 1.**

Diet compositions. Ratio, grams of fat: protein and carbohydrate.

Epilepsia © ILAE

# High-fat diets

## ► Caution! | Attention !

- ▶ Do not provide medications in liquid form | Aucune médication sous forme liquide
- ▶ Be careful with products that might contain carbohydrates
  - ▶ Lotion and sunscreen
  - ▶ Shampoo
  - ▶ Bath and hand soaps
  - ▶ Toothpaste
  - ▶ Bug spray
  - ▶ ChapStick

# High-fat diets

- ▶ Mechanism of action | Mécanisme d'action
  - ▶ Unknown | Incertain
    - ▶ Low glucose level?
    - ▶ Elevated ketone level?
    - ▶ Decrease mTOR activity?
    - ▶ Decrease neuronal excitation?
      - ▶ Ketone bodies inhibit presynaptic vesicular transporters
      - ▶ Acetoacetate inhibit quantum glutamate release from rat hippocampal slices

# High-fat diets: efficacy

- ▶ Traditional Ketogenic diet
  - ▶ Appears to work faster, typically within 2-4 weeks compared to VNS
  - ▶ Henderson 2006
    - ▶ Meta-analysis of 19 studies done in children; total of 1084 patients
    - ▶ Results
      - ▶ Decrease seizure frequency by > 90% in 1/3 of patients
      - ▶ Decrease seizure frequency by > 50% in 1/2 of patients
      - ▶ No influence of age, seizure type, or etiology
- ▶ Modified Atkins diet
  - ▶ Review article by Kossoff (2012)
    - ▶ 22 Publications on use of MAD in patients with epilepsy
    - ▶ Total of 280 patients
    - ▶ Seizure frequency at 6 months
      - ▶ 123 (44%) having > 50% seizure reduction compared to baseline
      - ▶ 72 (26%) having > 90% seizure reduction compared to baseline
  - ▶ Results similar to those described in the traditional KD

# High-fat diets: efficacy

- ▶ Efficacy | Efficacité
  - ▶ Other possible benefits | Autres bénéfices possibles
    - ▶ Improvement in development | Amélioration du développement
    - ▶ Improvement in behavior | Amélioration du comportement
    - ▶ Reduced dosage or discontinuation of anticonvulsants | Diminution des anticonvulsivants
      - ▶ Anticonvulsant medications stopped in ~ 20% of patients

# What about patients with Dravet syndrome?

- ▶ Caraballo (2005)
  - ▶ 20 children
  - ▶ Ketogenic diet 4:1 ratio
  - ▶ 65% had at least/au moins 50% decrease in seizure frequency/diminution de la fréquence des crises
  - ▶ 50% has at least/au moins 75% decrease in seizure frequency /diminution de la fréquence des crises
- ▶ Blackford (2013)
  - ▶ 20 children
  - ▶ Ketogenic diet 3:1 or 4:1 ratio
  - ▶ 65% had at least/au moins 50% decrease in seizure frequency /diminution de la fréquence des crises
  - ▶ 30% has at least/au moins 90% decrease in seizure frequency /diminution de la fréquence des crises

# Side effects | Effets secondaires

- ▶ Possible side effects:
  - ▶ Hypercholesterolemia
  - ▶ Mineral deficiencies
  - ▶ Acidosis
  - ▶ Constipation
  - ▶ Weight loss
  - ▶ Kidney stones
  - ▶ Growth retardation
  - ▶ Carnitine deficiency
  - ▶ Prolonged QT interval (selenium deficiency)
  - ▶ Osteopenia/Osteoporosis
- ▶ Most side effects treatable and/or preventable
- ▶ La majorité des effets secondaires sont prévenables et/ou traitables
  - ▶ Hypercholesterolemia: change ratio or fat composition ( $\uparrow$ MCT)
  - ▶ Growth retardation:  $\downarrow$  ratio
  - ▶ Weight loss:  $\uparrow$  caloric intake
  - ▶ Appropriate vitamin and mineral supplementation
    - ▶ Calcium, selenium, citrate, zinc, vitamin D, etc.
  - ▶ Avoid initial fast
  - ▶ Avoid fluid restriction
  - ▶ Use alternative diets

# Supplementation

Epilepsia, 50(2):304–317, 2009  
doi: 10.1111/j.1528-1167.2008.01765.x

## SPECIAL REPORT

### Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group

**Table 4. Supplementation recommended for children receiving the KD**

Universal recommendations
Multivitamin 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 (Carnitor)
MCT oil or coconut oil (source of MCT)
Salt (sodium to add to modular formulas if used for greater than age 1 year)

All supplements listed should be provided as carbohydrate-free preparations whenever possible.

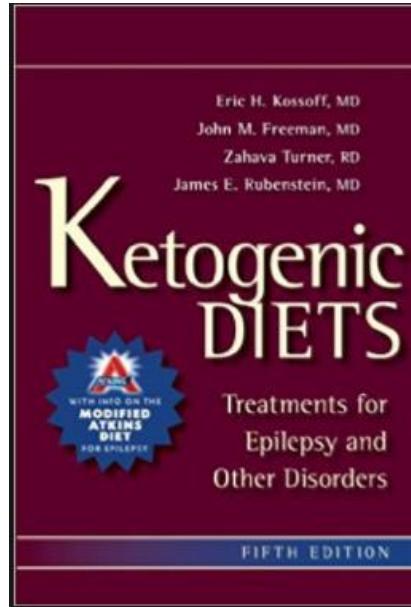
# Diet discontinuation

- ▶ Consensus is to try diet for at least 3 months | Tenter pour au moins 3 mois
- ▶ When to discontinue the diet? | Quand cesser?
  - ▶ Can be stopped abruptly at any time in case of medical emergency
  - ▶ Diet usually continued for at least 2 years if tolerated and beneficial
  - ▶ Stopped progressively by decreasing ratio
  - ▶ Long-lasting benefits reported even after discontinuation of the diet



IN 1993 THE KETOGENIC DIET CURED  
CHARLIE ABRAHAMS' EPILEPSY

OUR STORY



Want to read  
more?  
Vous voulez en  
savoir plus?



Merci!  
Thank You!

# References

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