



# **Update : Epilepsie bij kinderen**

**Typische casuïstiek**

**Behandelingsopties**



# overzicht

- Indeling meest frequente epilepsietypes bij kinderen en behandelingsopties
- Neonatale convulsies
- Febriele convulsies
- Behandeling : anti-epileptica



# Klassieke indeling

## Epileptische aanvallen

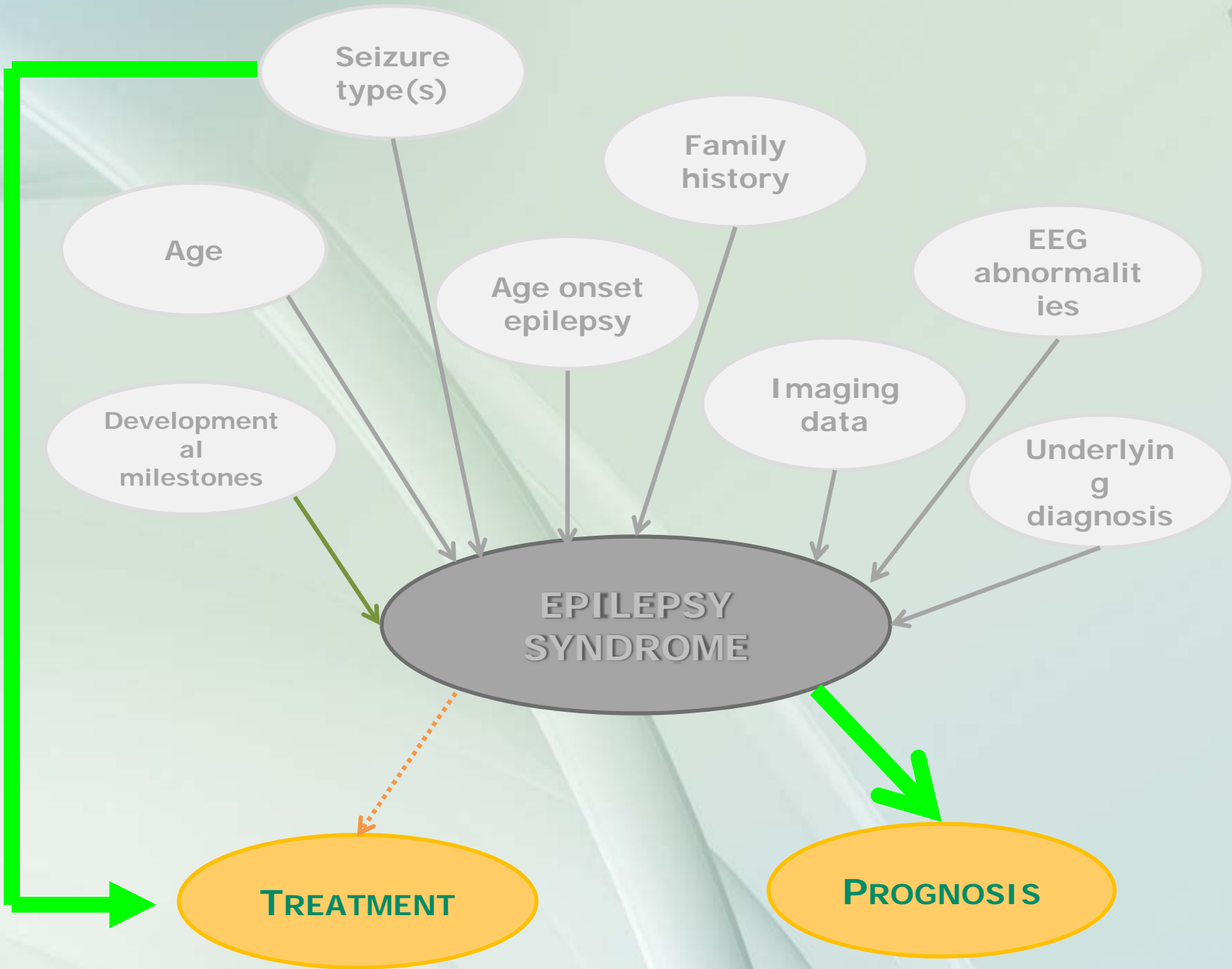
- Semeiologie aanvallen

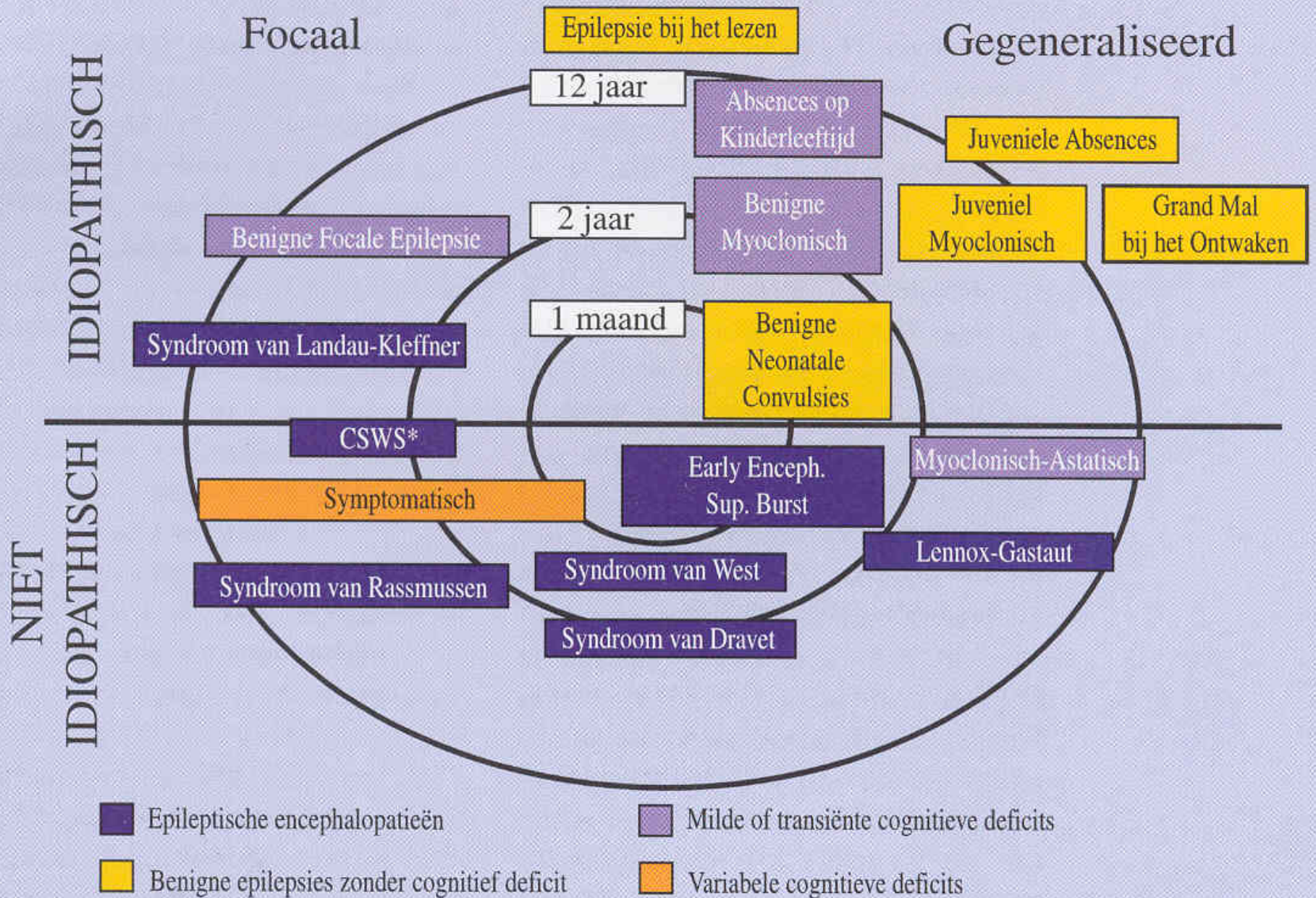
**Partieel versus gegeneraliseerd**

## Epilepsie syndromen

- Type epileptische aanvallen
- EEG afwijkingen
- Leeftijd
- Beeldvorming
- Genetica
- Metabool onderzoek

**Symptomatisch versus idiopathisch**





\* CSWS (Continuous spikes and waves during slow sleep)

# Groepering syndromen



- **Focale idiopatische epilepsie**
  - Rolandische epilepsie
  - Occipitale epilepsie
- **Focale symptomatische epilepsie**
  - Focale corticale malformaties
  - Mesiaal temporaal sclerose
- **Gegeneraliseerde idiopatische epilepsie**
  - Absence epilepsieën
  - Juvenile myoclonie epilepsie
  - Idiopatische gegeneraliseerde epilepsie
- **Gegeneraliseerde symptomatische epilepsie**
  - West syndroom
  - Lennox Gastaut syndroom
  - Myoclonie astatische epilepsie
  - Severe myoclonic epilepsy of infancy
- **Febriële convulsies**
- **Neonatale epilepsie**



NEONATES → INFANTS → CHILDREN → ADOLESCENTS

**BFNS** | **BFNIS** | **BFIS**

**FS** | **GEFS+**

**IGE**

**CAE** | **JAE**

**JME**

**BCOE (P)** | **BCOE (G)**

**BCECTS**

**CSWSS**

<b>EMEE</b> <b>EIEE</b>	<b>WEST</b> <b>MIGRATING PARTIAL</b> <b>SIMFE</b>	<b>LENOX GASTAUT SYNDROME</b> <b>MYOCLONIC ASTATIC EPILEPSY</b> <b>SEVERE MYOCLONIC EPILEPSY OF INFANCY</b>
----------------------------	---	---



- Frequent bij jonge kinderen
- **'epileptische encephalopathie'**
  
- Frequent *verschillende* gegeneraliseerde epileptische aanvallen
  - Myoclonie schokken
  - Infantiele spasmes
  - Tonische aanvallen
  - Atypische absences
  - Astatische aanvallen
  - Tonische clonische aanvallen
- Frequent refractair
- Negatief effect op cognitieve evolutie



# Frequente syndromen

- Neonatale syndromen met burst suppressie op EEG
- **West syndroom**
- **Severe Myoclonic epilepsy of infancy**
- **Lennox Gastaut epilepsie**
- **Myoclone Astatische epilepsie**
- Multifocale epilepsie
- Migrating epilepsy of infancy
- Syndromes with continuous spikes and waves during sleep



# Neonatale epilepsie

*“Any stereotypic movement  
may be a manifestation  
of a seizure disorder”*



## Patterns of seizure activity in the newborn

<b>Movement pattern</b>	<b>Frequency (%)</b>
Clonic	50
Tonic	20
Subtle	10–35 depending on maturity
Myoclonic	5



## Cause, incidence and outcome of neonatal convulsions in term infants<sup>1,4</sup>

Aetiological factor	Incidence (%)	Poor outcome (%) <sup>*</sup>
Asphyxia	38-40	50
Cerebral arteriovenous infarction	20	0
Intracranial haemorrhage	12-20	13
Congenital cerebral anomaly	5-10	100
Hypoglycaemia/hypocalcaemia	3-19	**
Infection	3-20	**
Inborn error of metabolism	1	**
Unknown cause	10-13	0

<sup>\*</sup>Refers to moderate and severe neurodevelopmental abnormality.

<sup>\*\*</sup>Numbers too small to make meaningful predictions.

# 'Frequente' oorzaken van neonatale convulsies



**Pyridoxine deficiency**

AASA urine, pipecolic acid, ALDH7A1

**Pyridoxal phosphate deficiency**

**Folinic acid deficiency**

**Non ketotic hyperglycinemie**

AA

**Biotinidase deficiency**

biotinidase assay

**Sulphite oxidase deficiency**

**Molybdene cofactor deficiency**

sulphite test urine, homocystein

**Serine metabolism**

AA

**CDG syndromes**

sialotransferrines electrophoresis

**Zellweger syndrome**

ELCFA

**Ceroid lipofuscinosis**

skin biopsy



# Genetics in *idiopathic* neonatal seizures

- **Benign familial neonatal seizures**
  - K channel (KCNQ2/KCNQ3 )
- **Benign familial neonatal infantile seizures**
  - Na channel (SCN2A)
- **Early infantile epileptic encephalopathy (Othahara syndrome)**
  - K channel KCNQ2 (gain of function)
  - Glut 1 mutations
  - Syntaxin binding protein1 (Munc 18.1)



Sankar and Painter, Neurology 2005:

***After all these years, we still love what doesn't work***

**Neonatal seizures without an obvious cause:**

**Trial with pyridoxine 100mg IV**

**Start metabolic/genetic workup  
(Amino acid and urea urgent)**



## Dosage regimens for first-, second- and third-line anticonvulsants in the neonatal period

	Loading dose	Second loading dose if first unsuccessful	Maintenance dose
Phenobarbitone	20 mg/kg by slow iv injection	10 mg/kg iv	2.5–5 mg/kg od
Phenytoin	20 mg/kg iv over 20 min		Not recommended
Midazolam	150–200 µg/kg iv infusion		1 µg/kg/min iv infusion, increasing to 5 µg/kg/min until favourable response
Lidocaine*	2 mg/kg iv over 10 min		6 mg/kg/h for 6 h iv, then 4 mg/kg/h for 12 h, then 2 mg/kg/h for 12 h
Lorazepam	0.05–0.1 mg/kg by slow iv injection		
Diazepam	0.3–0.4 mg/kg iv over 3–5 min		

\*Lidocaine should not be used if the infant has previously been treated with phenytoin.

**When to start? One clinical seizure, abnormal EEG? Status epilepticus?**

**Outcome parameter ? Clinical, EEG, longterm (absence of epilepsy)?**



	Clinical Seizure	No seizure
Epileptic EEG Ictal tracé		<b>Electro Clinical dissociation</b>
Normal EEG	<b>Electro Clinical dissociation</b>	



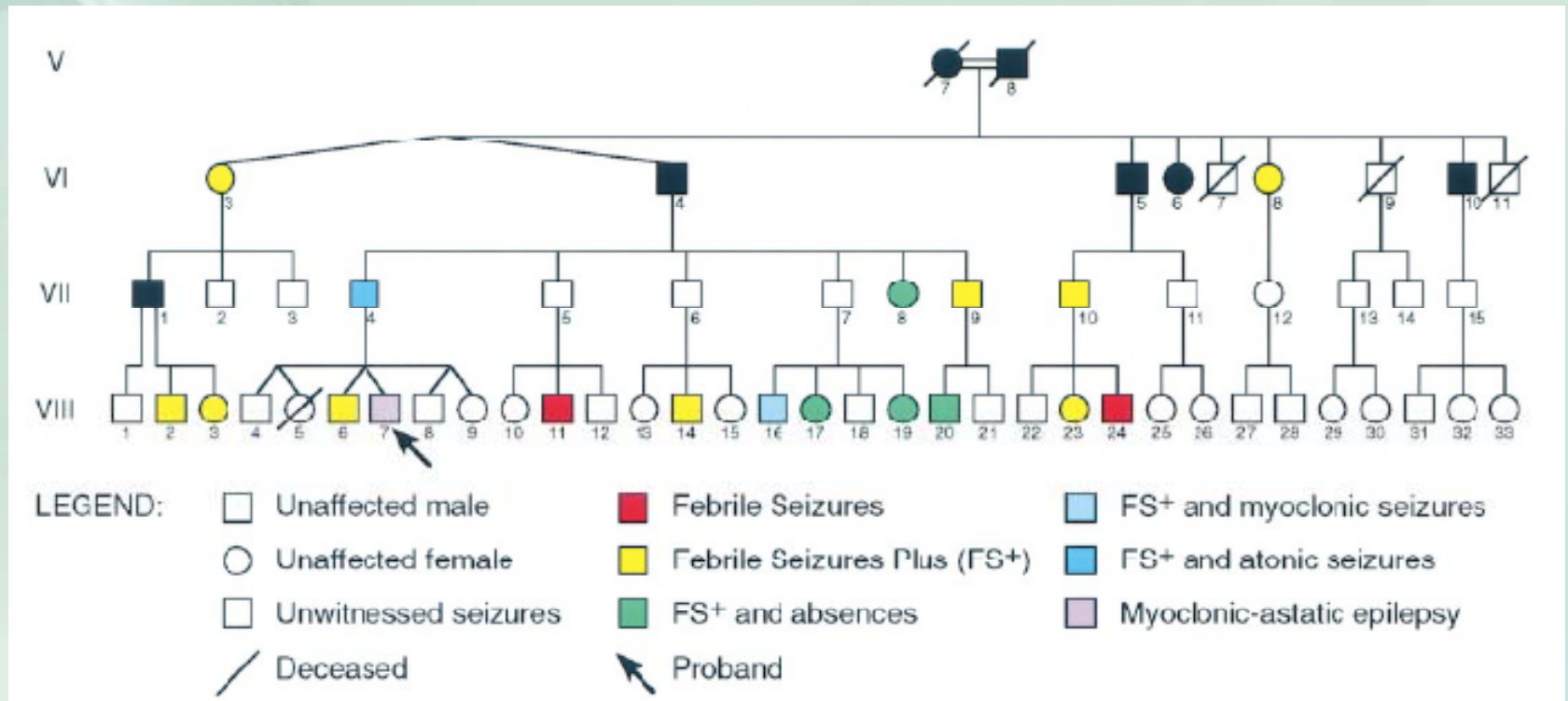
# Febriële convulsies



# Febriële convulsies : Frequent !

- 'Simpele'
  - Kortdurend (<15 minuten)
  - Gegeneraliseerd (tonic/clonic)
  - Geen recidief binnen zelfde koortsepisode (24 h)
  - Geen postictale (gelateraliseerde tekens)
  
- 'Complexe'
  - Langere duur
  - Verschillende aanvallen binnen zelfde koortsepisode
  - Focale aanvallen
  - Postictale gelateraliseerde tekens

# “Generalized epilepsy and febrile seizures plus”



I Scheffer, S Berkovic, Brain 1997, 120:479-490

# GEFS+



## Generalized epilepsy – Febrile seizures Plus

- 'Familie diagnose'
- Autosomaal dominant
- Febriële en afebriële aanvallen bij één patient en binnen één familie
- Vooral gegeneraliseerde aanvallen

cave

- Niet alleen goedaardige epilepsie syndromen



**Table 1: Monogenic childhood epilepsies**

K <sup>+</sup> channel	KCNQ2 KCNQ3	Benign familial neonatal seizures	BFNS
Na <sup>+</sup> channel	SCN2A SCN1B SCN1A	Benign familial neonatal infantile seizures Generalised epilepsy/febrile seizures+ Generalised epilepsy/febrile seizures+ Severe myoclonic epilepsy of infancy	BFNIS GEFS+ GEFS+ SMEI
GABA receptor	GABRG2  GABRA1	Generalised epilepsy/febrile seizures+ Childhood absence epilepsy Childhood absence epilepsy Autosomal dominant juvenile myoclonic epilepsy	GEFS+ CAE CAE ADJME
Cl <sup>-</sup> channel	CLCN2	Idiopathic generalised epilepsy	IGE (JME)
Nicotinic Acetylcholine Receptor	CHRNA4 CHRNA2 CHRNA2	Autosomal dominant nocturnal frontal lobe epilepsy	ADNFLE
LG11 (~K <sup>+</sup> channel)	LG11	Autosomal dominant partial epilepsy with auditory features	ADPEAF

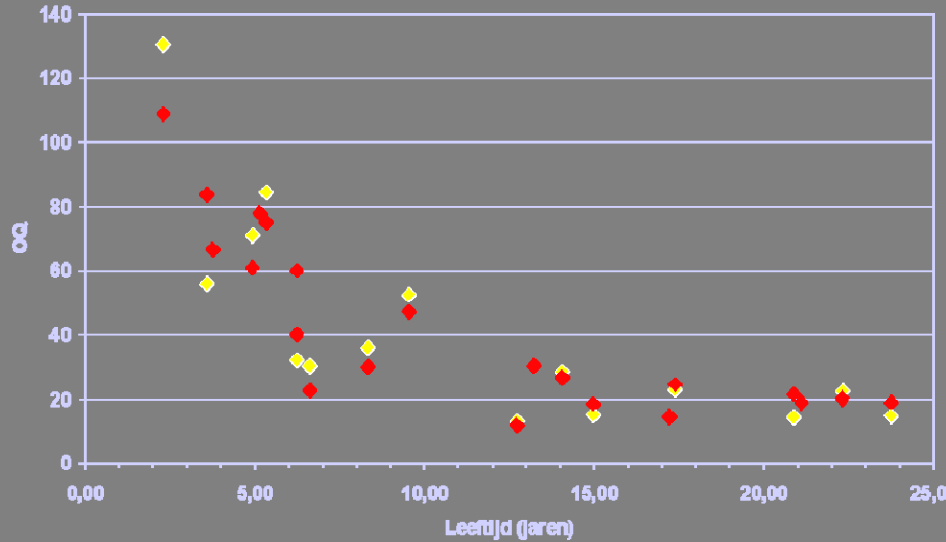


# Epileptische syndromen met febrile convulsies als eerste aanvalstype

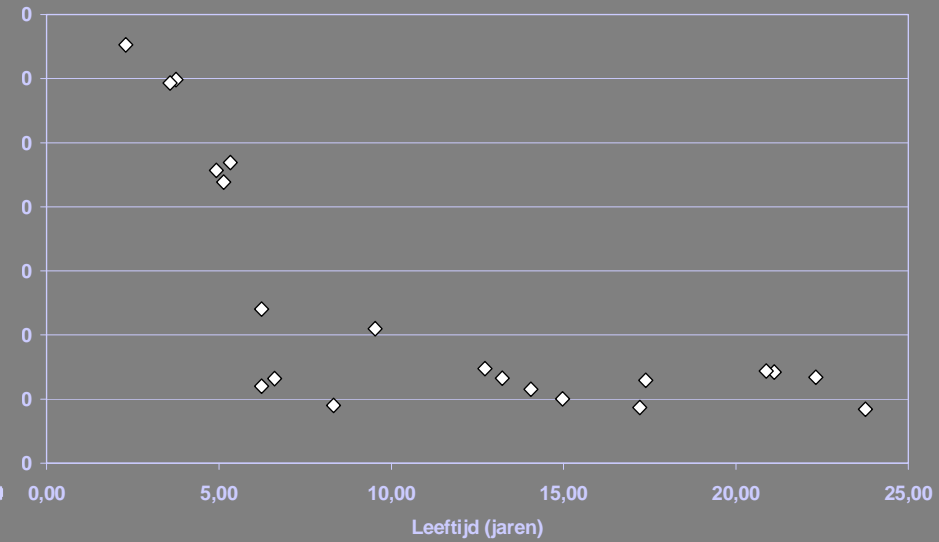
- GEFS +
- Severe myoclonic epilepsy of infancy: **Dravet syndrome**
- HHE syndrome
- Mesial-temporal sclerosis

# Severe Myoclonic epilepsy of infancy (SCN1A+)

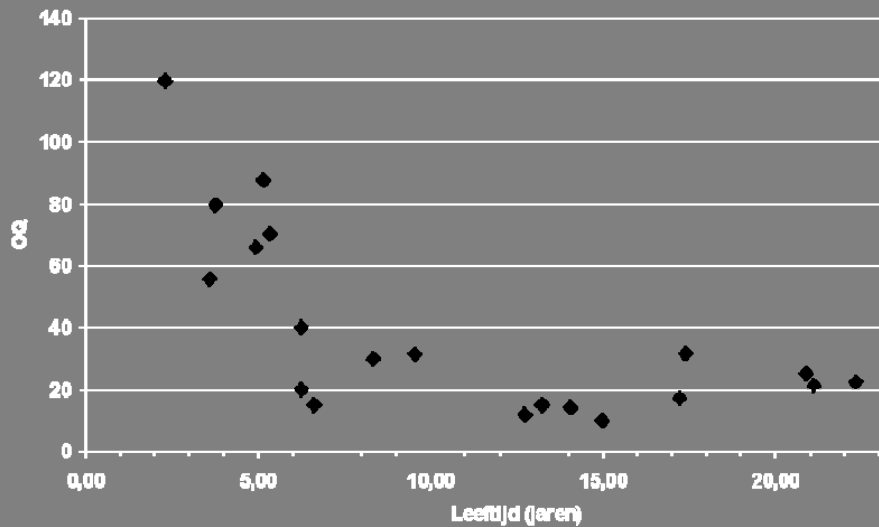
MOTORIEK: geschat ontwikkelingsniveau (OQ)



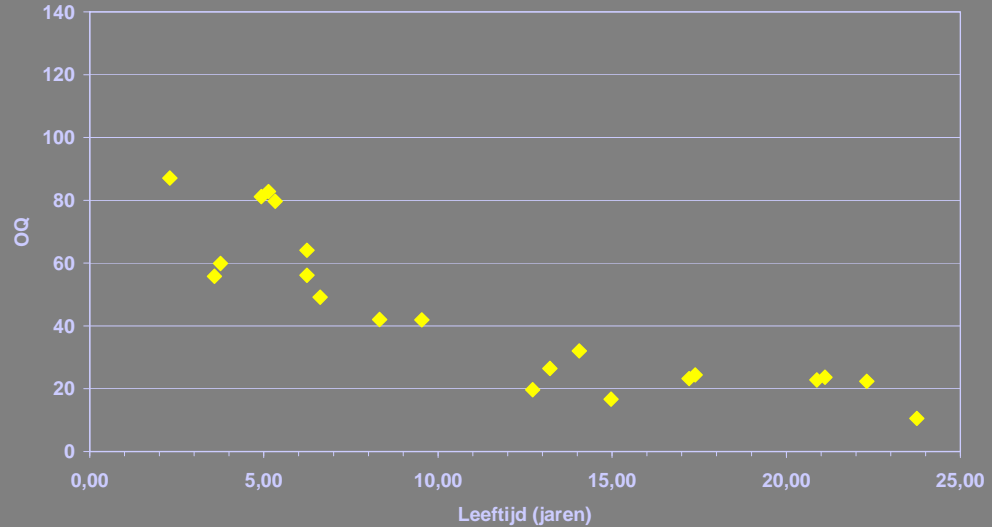
COGNITIE: geschat ontwikkelingsniveau (OQ)



TAAL & COMMUNICATIE: geschat ontwikkelingsniveau (OQ)



SOCIALE ONTWIKKELING & SPEL: geschat ontwikkelingsniveau (OQ)





## **Febriële convulsies en mesiaal temporaal sclerose**

- **MTS : 30% langdurige febriële convulsies als kind**
- **MTS gevolge van langdurige aanvallen?**

# Hippocampaal oedeem na langdurige febriële aanval





## Acute behandeling: zelden nodig

### Convulsieve aanval :

> 90% van de aanvallen stopt < *2 minuten*

*Meerderheid (febriële) convulsies stopt binnen de minuut*

**convulsieve aanvallen > 7-10 min: geen spontane stop  
meer en risico op status epilepticus**

*Acute behandeling aangewezen indien  
convulsies > 3 minuten duren*



## Acute behandeling: Benzodiazepines

- werkingsmechanisme : + Gaba receptor
- Snelle penetratie naar de hersenen
- Korte halfwaarde tijd
- Cave : sedatie, hypotensie, respiratoire depressie
- **Lorazepam, diazepam, clonazepam, midazolam**

# Eerste lijn



- Diazepam (Valium) rectaal
  - 0.3 mg/kg/dosis
  - Praktisch : Stesolid 5 / 10 mg rectioles
- Lorazepam (Temesta expedit) sublinguaal
  - 0.1 mg/kg/dosis
  - Praktisch : Temesta Expedit 1 mg – 2.5 mg
  - Oplossing (Amp 4 mg/1ml) kan ook intrarectaal
- Clonazepam (Rivotril druppels) oraal
  - 0.2 mg/kg/dosis
  - Praktisch : rivotril druppels 1 druppel = 0.1 mg
- Midazolam (Dormicum) intranasaal
  - Dosis : 0.2mg/kg/dosis
  - Praktisch: domicum amp 5mg/5ml
  - Toediening niet eenvoudig (cave congestie neusmucosa)

## Intraveneus benzodiazepines

**Diazepam 0.3 mg/kg**

**Lorazepam 0.1mg/kg**

**Clonazepam 0.1mg/kg**



# Profylactische behandeling?

- **herval risico ? 30-40%**

- *leeftijd bij eerste aanval + + +*
- Familiale voorgeschiedenis febrile convulsies
- lagere temperatuur bij aanval
- Complexe febrile convulsies
- Abnormale ontwikkeling

- **(sub)acute sequellen?**

Secondaire hersenschadebrain pas na 30 minuten convulsies

- **epilepsie na recurrenente febrile convulsies?**

leeftijd 5 :            epilepsie risico 2%  
leeftijd 25 :           epilepsie risico 7%

complexe > simpele  
abnormale ontwikkeling : +30%



## *Preventie van febrile convulsies voorkomt epilepsie niet*

- **Phenobarbital** 3mg/kg/day
- **Natrium valproate** 20 mg/kg/day
- Niet effectief : Phenytoin, Carbamazepine
- Andere anti-epileptica niet echt getest
- Cave intermittent benzodiazepines (maskering intracraniele infecties)

# behandelingsmogelijkheden



- Anti-epileptische medicatie
- Epilepsie chirurgie
- Nervus vagus stimulatie
- Ketogeen dieet

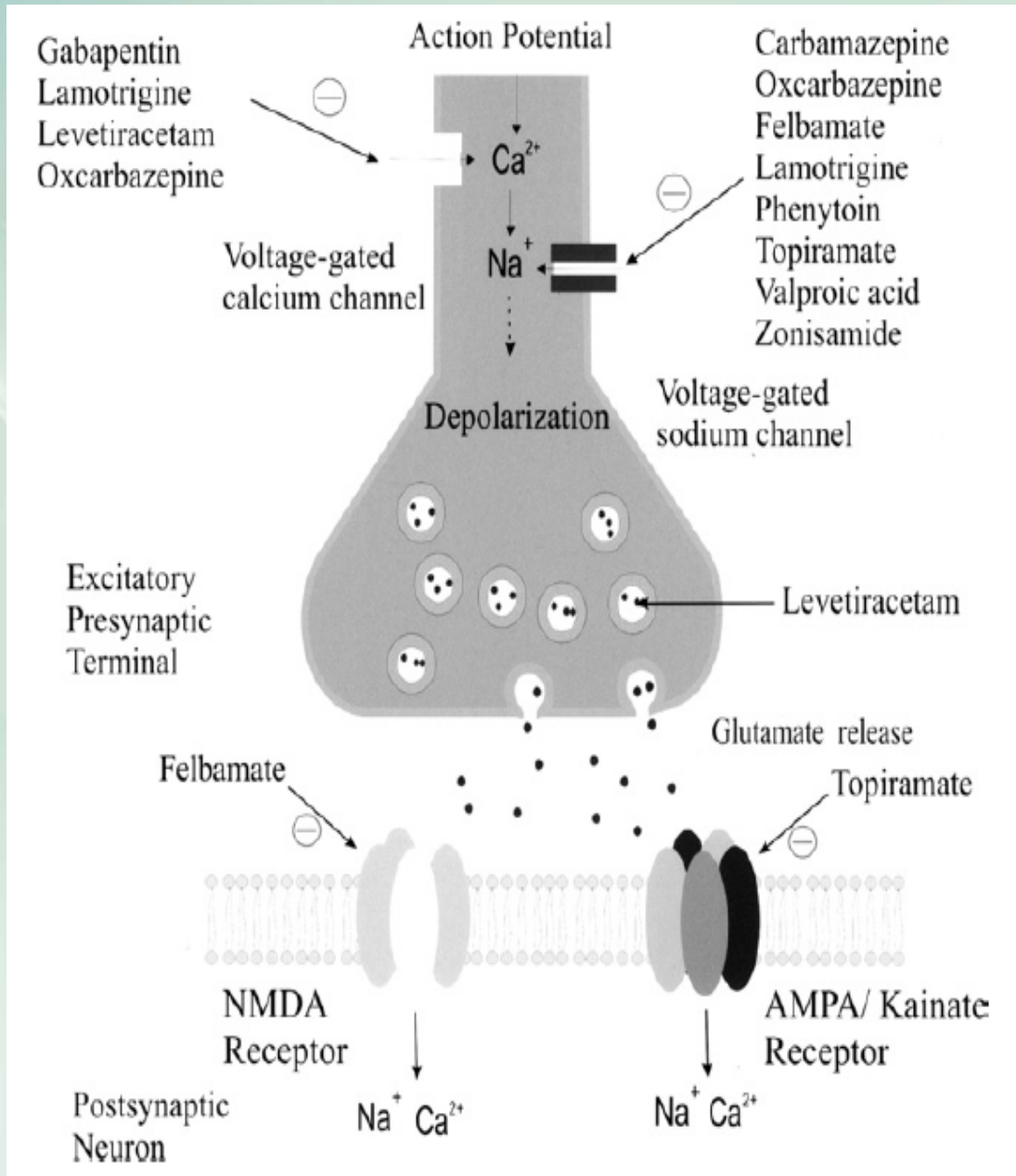


Epilepticus sic curabitur ?

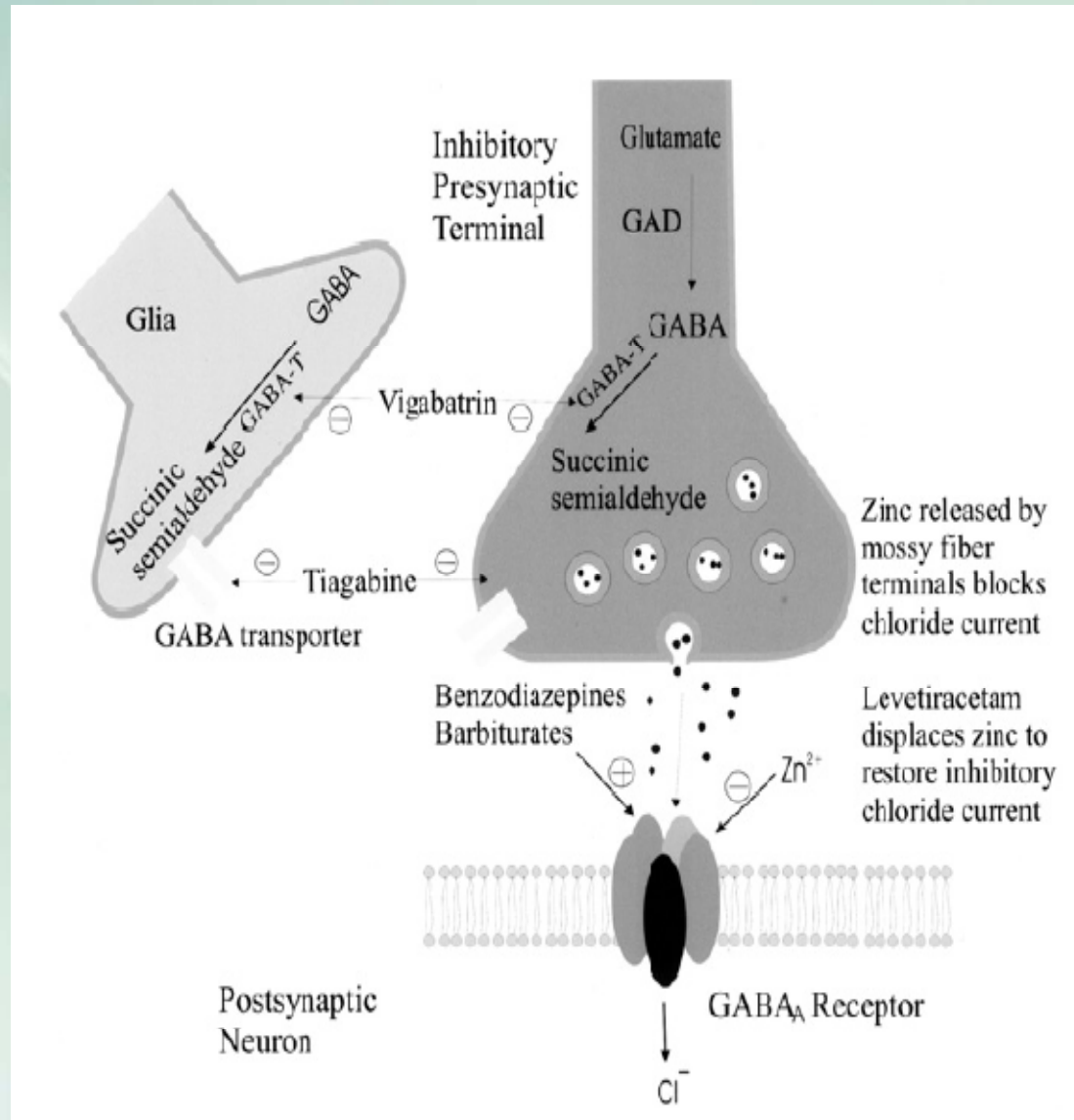


# Anti-epileptic drugs : AEDs

- Oude klassiekers : phenobarbital, fenytoin, primidone
- Standaard : carbamazepine, Na valproaat, ethosuximide, sulthiame
- Nieuwere : vigabatrine, lamotrigine, oxcarbaepine, topiramate, tiagabine, gabapentin, levetiracetam, felbamate, zonisamide, stiripentol, lacosamide, pregabaline, rufinamide, perampanel, retigabine,...
- Benzodiazepines



Excitatory synaps



## Inhibitory synaps

	AAN <sup>b</sup>		SIGN		NICE <sup>a</sup>				ILAE <sup>b</sup>							
	Partial/Mixed Monotherapy	CAE	Partial & 2 <sup>nd</sup> generalized	1 <sup>st</sup> generalized	CAE	JAE	JME	GTCS	Partial onset			GTCS		CAE	BECTS	JME
									Adults	Children	Elderly	Adults	Children			
CBZ	A		1st					1st	A	C	C	C	C	E	C	E
CZP								2nd	D	E	E	E	E	E	E	D
DZP									E	E	E	E	E	E	E	E
ESM					1st				E	E	E	E	E	E	E	E
FBM									E	E	E	E	E	E	E	E
GBP	A	No							C	E	A	D	E	F	D	E
LEV	No	No			2nd	2nd	2nd	2nd	E	E	E	E	E	E	E	D
LTG	A	B	1st	1st	1st <sup>c</sup>	1st <sup>c</sup>	1st <sup>c</sup>	1st <sup>c</sup>	C	D	A	C	E	C	E	D
LZP									E	E	E	E	E	E	E	E
OXC	A	No	1st						C	A	E	C	D	-	E	E
PB	A								C	C	E	C	C	E	E	E
PGB									E	E	E	E	E	E	E	E
PHT	A								A	C	D	C	C	E	E	E
PRM									D	E	E	E	E	E	E	E
TGB	No	No							E	E	E	E	E	-	E	E
TPM	A	No			2nd	2nd	2nd	1st <sup>c</sup>	C	C	D	C	C	E	E	D
VGB									C	D	E	D	E	-	E	E
VPA	A		1st	1st	1st	1st	1st	1st	B	C	D	C	C	C	C	D
ZNS	No	No							E	E	E	E	E	E	E	D

<sup>a</sup> Review of Guideline expected to start October 2008 (Review Proposal - November 2007)

<sup>b</sup> A = AED established efficacious or effective as initial monotherapy; B = probably; C = possibly; D = potentially; E = No RCT data available; F = ineffective or significant risk of seizure aggravation;

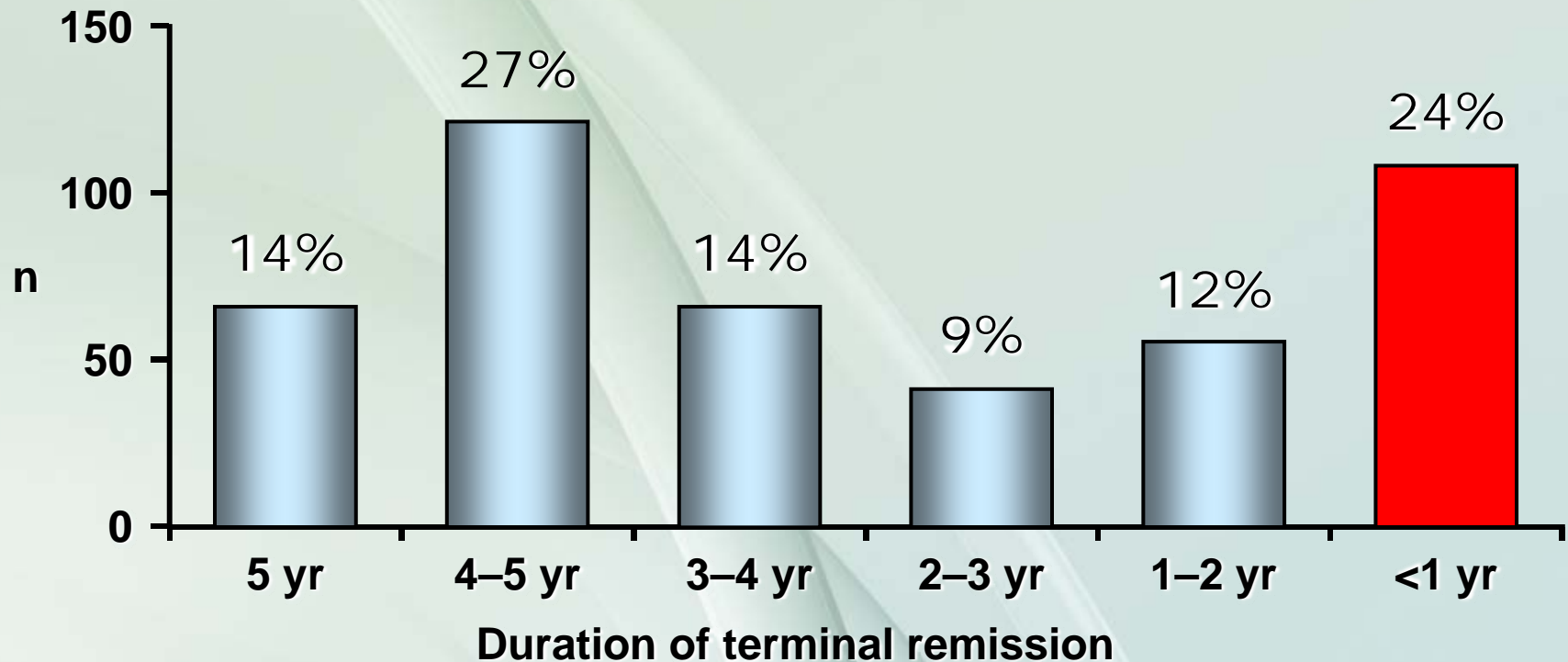
- = may precipitate or aggravate absence seizures

<sup>c</sup> Should be used as 1<sup>st</sup> choice under circumstances as outlined in NICE Technology Appraisal of newer AEDs

# Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood

Willem F. M. Arts,<sup>1</sup> Oebele F. Brouwer,<sup>6</sup> A. C. Boudewijn Peters,<sup>4</sup> Hans Stroink,<sup>8</sup> Els A. J. Peeters,<sup>7</sup>  
Paul I. M. Schmitz,<sup>3</sup> Cees A. van Donselaar<sup>5</sup> and Ada T. Geerts<sup>2</sup>

## Outcome of 453 children with newly diagnosed epilepsy at 5 years of follow-up





## Optimaal anti-epilepticum?

Effectief

Breed spectrum?

Geen toename van de aanvallen

**Monotherapie**

**Weinig bijwerkingen**

**Geen negatieve invloed op cognitieve ontwikkeling**

**Kindvriendelijke toediening, BID**

**Voorspelbare en beheersbare farmacokinetiek**



# **National Institutes for Health and Clinical Excellence**

**NICE guidelines Oct 2004**

<http://guidance.nice.org.uk/>

**Table 1 Drug options by seizure type**

<i>Seizure type</i>	<i>First-line drugs</i>	<i>Second-line drugs</i>	<i>Other drugs that may be considered</i>	<i>Drugs to be avoided (may worsen seizures)</i>
Generalised tonic-clonic	Carbamazepine <sup>a</sup> Lamotrigine <sup>b</sup> Sodium valproate Topiramate <sup>a,b</sup>	Clobazam Levetiracetam Oxcarbazepine <sup>a</sup>	Acetazolamide Clonazepam Phenobarbital <sup>a</sup> Phenytoin <sup>a</sup> Primidone <sup>a,c</sup>	Tiagabine Vigabatrin
Absence	Ethosuximide Lamotrigine <sup>b</sup> Sodium valproate	Clobazam Clonazepam Topiramate <sup>a</sup>		Carbamazepine <sup>a</sup> Gabapentin Oxcarbazepine <sup>a</sup> Tiagabine Vigabatrin
Myoclonic	Sodium valproate Topiramate <sup>a</sup>	Clobazam Clonazepam Lamotrigine Levetiracetam Piracetam		Carbamazepine <sup>a</sup> Gabapentin Oxcarbazepine <sup>a</sup> Tiagabine Vigabatrin
Tonic	Lamotrigine <sup>b</sup> Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate <sup>a</sup>	Acetazolamide Phenobarbital <sup>a</sup> Phenytoin <sup>a</sup> Primidone <sup>a,c</sup>	Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup>
Atonic	Lamotrigine <sup>b</sup> Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate <sup>a</sup>	Acetazolamide Phenobarbital <sup>a</sup> Primidone <sup>a,c</sup>	Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup> Phenytoin <sup>a</sup>
Focal with/without secondary generalisation	Carbamazepine <sup>a</sup> Lamotrigine <sup>b</sup> Oxcarbazepine <sup>a,b</sup> Sodium valproate Topiramate <sup>a,b</sup>	Clobazam Gabapentin Levetiracetam Phenytoin <sup>a</sup> Tiagabine	Acetazolamide Clonazepam Phenobarbital <sup>a</sup> Primidone <sup>a,c</sup>	

a Hepatic enzyme-inducing AED.

b Should be used as a first choice under circumstances as outlined in the NICE technology appraisal of newer AEDs for children – see page 7

c Should rarely be initiated – if a barbiturate is required, phenobarbital is preferred.

Table 3 summarises licensing status in July 2004. For current details on licensing, see the Summary of Product Characteristics for each drug and/or the *British National Formulary*.

**Table 2 Drug options by epilepsy syndrome**

<i>Epilepsy syndrome</i>	<i>First-line drugs</i>	<i>Second-line drugs</i>	<i>Other drugs</i>	<i>Drugs to be avoided (may worsen seizures)</i>
Childhood absence epilepsy	Ethosuximide Lamotrigine <sup>b</sup> Sodium valproate	Levetiracetam Topiramate <sup>a</sup>		Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup> Phenytoin Tiagabine Vigabatrin
Juvenile absence epilepsy	Lamotrigine <sup>b</sup> Sodium valproate	Levetiracetam Topiramate <sup>a</sup>		Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup> Phenytoin <sup>a</sup> Tiagabine Vigabatrin

**Table 2 Drug options by epilepsy syndrome *continued***

<i>Epilepsy syndrome</i>	<i>First-line drugs</i>	<i>Second-line drugs</i>	<i>Other drugs</i>	<i>Drugs to be avoided (may worsen seizures)</i>
Juvenile myoclonic epilepsy	Lamotrigine <sup>b</sup> Sodium valproate	Clobazam Clonazepam Levetiracetam Topiramate <sup>a</sup>	Acetazolamide	Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup> Phenytoin <sup>a</sup> Tiagabine Vigabatrin
Generalised tonic-clonic seizures only	Carbamazepine <sup>a</sup> Lamotrigine <sup>b</sup> Sodium valproate Topiramate <sup>a,b</sup>	Levetiracetam	Acetazolamide Clobazam Clonazepam Oxcarbazepine <sup>a</sup> Phenobarbital <sup>a</sup> Phenytoin <sup>a</sup> Primidone <sup>a,c</sup>	Tiagabine Vigabatrin
Focal epilepsies: cryptogenic, symptomatic	Carbamazepine <sup>a</sup> Lamotrigine <sup>b</sup> Oxcarbazepine <sup>a,b</sup> Sodium valproate Topiramate <sup>a,b</sup>	Clobazam Gabapentin Levetiracetam Phenytoin <sup>a</sup> Tiagabine	Acetazolamide Clonazepam Phenobarbital <sup>a</sup> Primidone <sup>a,c</sup>	
Infantile spasms	Steroids <sup>d</sup> Vigabatrin <sup>b</sup>	Clobazam Clonazepam Sodium valproate Topiramate <sup>a</sup>	Nitrazepam	Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup>
Benign epilepsy with centrotemporal spikes	Carbamazepine <sup>a</sup> Lamotrigine <sup>b</sup> Oxcarbazepine <sup>a,b</sup> Sodium valproate	Levetiracetam Topiramate <sup>a</sup>	Sulthiame <sup>e</sup>	
Benign epilepsy with occipital paroxysms	Carbamazepine <sup>a</sup> Lamotrigine <sup>b</sup> Oxcarbazepine <sup>a,b</sup> Sodium valproate	Levetiracetam Topiramate <sup>a</sup>		





Severe myoclonic epilepsy of infancy	Clobazam Clonazepam Sodium valproate Topiramate <sup>a,b</sup>	Levetiracetam Stiripentol <sup>e</sup>	Phenobarbital <sup>a</sup>	Carbamazepine <sup>a</sup> Lamotrigine Oxcarbazepine <sup>a</sup> Vigabatrin
Continuous spike wave of slow sleep	Clobazam Clonazepam Ethosuximide Lamotrigine <sup>b</sup> Sodium valproate Steroids <sup>d</sup>	Levetiracetam Topiramate <sup>a</sup>		Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup> Vigabatrin
Lennox–Gastaut syndrome	Lamotrigine <sup>b</sup> Sodium valproate Topiramate <sup>a,b</sup>	Clobazam Clonazepam Ethosuximide Levetiracetam	Felbamate <sup>e</sup>	Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup>
Landau–Kleffner syndrome	Lamotrigine <sup>b</sup> Sodium valproate Steroids <sup>d</sup>	Levetiracetam Topiramate <sup>a</sup>	Sulthiame <sup>e</sup>	Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup>
Myoclonic astatic epilepsy	Clobazam Clonazepam Sodium valproate Topiramate <sup>a,b</sup>	Lamotrigine Levetiracetam		Carbamazepine <sup>a</sup> Oxcarbazepine <sup>a</sup>



## **Focal idiopathic and symptomatic**

**Carbamazepine**

**Oxcarbazepine**

**Na Valproaat**

**Levetiracetam**

**Lamotrigine**

**Topiramate**

**Sulthiame**



# Generalized idiopathic and symptomatic

Na valproaat

Topiramaat

Levetiracetam

Lamotrigine

Cave carbamazepine/oxcarbazepine



## **Speciale situaties**

**Infantiele spasms :**

**vigabatrine  
ACTH/prednisone  
topiramaat**

**Febriële convulsies**

**geen behandeling  
Na valproaat**

**Neonatale convulsies**

**phenobarbital  
phenytoin**



# Nieuwer concept

**Start** : Breed spectrum anti-epileptica

- **Valproate, Lamotrigine, Levetiracetam, Topiramate (zonisamide)**
- Duidelijk partiële aanvallen :  
**carbamazepine/oxcarbazepine, sulthiame**
- Absence seizures : **ethosuximide**

**Tweede stap: monotherapy met ander breedspectrum**

**Derde stap: 'rationele polytherapie'  
epilepsie chirurgie?**



# Breedspectrum anti-epileptica

- Effectief voor verschillende aanvalstypes
- *Geen toename van de aanvallen*
- *Minimale bijwerkingen*

*Therapeutische beslissing hangt meer af van bijwerkingsprofiel en patientkarakteristieken*

# Determining factors in the choice of optimal AED in childhood epilepsy (1)



- **Epilepsy related**
  - Seizure type
  - **Epilepsy syndrome**
  - EEG abnormalities
  
- **Patient related**
  - Age
  - Underlying paediatric and neurological diagnosis
  - Co-morbidities
  - Cognitive behaviour and behavioural state of the child

# Determining factors in the choice of optimal AED in childhood epilepsy (2)



- **Drug related**
  - Working mechanism
  - **Side-effect profile**
  - No/little effect on cognition and behaviour
  - No aggravation of seizures
  - **No/little interaction** with other AEDs and other drugs
  - Adequate formula available for (young) children
  - Intravenous formula available
  
- **Regulatory issues**
  - Registration
  - Cost
  - Reimbursement issues



# Toename aanvallen door anti-epileptica

**Table 2. Reported AED-induced aggravation of seizures or epilepsy syndromes**

Seizure Type /Syndrome	CBZ	OXC	PHT	LTG	VPA	GBP	VGB	TGB	BDZ
Absences	+++	+	+++		+	+	++	+	
Myoclonic	+++	+	+++	+		+	+		
JME	++	+	++	+					
LGS/MAE	++	+	++	+		+	++		++
BECTS	++			+	+				
SMEI	+			++			+		
LKS/ESES	+		+						
ULD			+						

Potential or evidence for aggravation: + limited; ++ moderate; +++ significant.

## Abbreviations:

AED = Antiepileptic drug

BDZ = Benzodiazepine

BECTS = Benign epilepsy of childhood with centro-temporal spikes

CBZ = Carbamazepine,

ESES = Electrical status epilepticus of sleep

GBP = Gabapentin

JME = Juvenile myoclonic epilepsy

LGS = Lennox-Gastaut syndrome

LKS = Landau-Kleffner syndrome

LTG = Lamotrigine,

MAE = Myoclonic atstatic epilepsy

OXC = Oxcarbazepine

PHT = Phenytoin

SMEI = Severe myoclonic epilepsy of infancy

TGB = Tiagabine

ULD = Unverricht-Lundborg disease

VGB = Vigabatrin

VPA = Valproic acid

# Toename aanvallen tijdens RCT

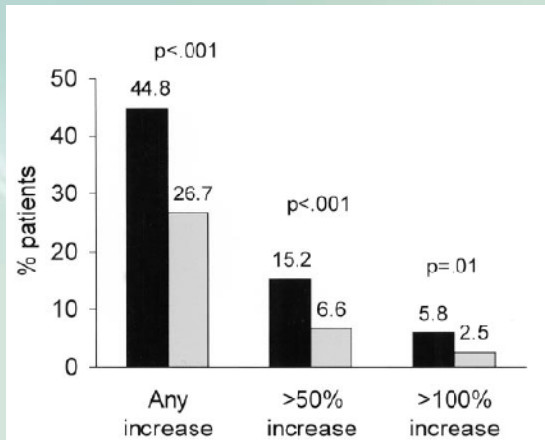


Figure 4. Percentage of patients in levetiracetam clinical trials experiencing an increase in seizure frequency. Black bars = placebo (n = 310); gray bars = levetiracetam (n = 589).

Levetiracetam

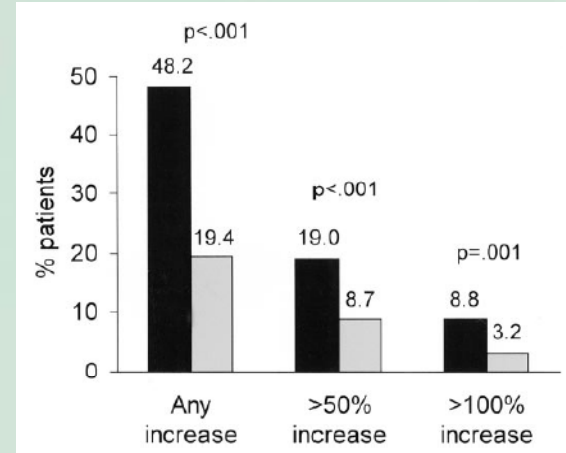


Figure 3. Percentage of patients in topiramate clinical trials experiencing an increase in seizure frequency. Black bars = placebo (n = 216); gray bars = topiramate (n = 527).

Topiramaat

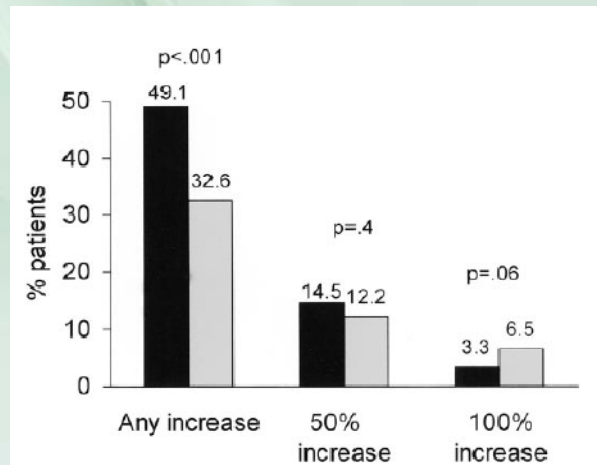


Figure 2. Percentage of patients in tiagabine clinical trials experiencing an increase in seizure frequency. Black bars = placebo (n = 275); gray bars = tiagabine (n = 491).

Tiagabine



# Idiosyncratic reactions

## Idiosyncratic Reactions: Older AEDs

Reaction	CBZ	ETX	PB	PHT	VPA
Agranulocytosis	X	X	X	X	X
Stevens-Johnson	X	X	X	X	X
Aplastic anemia	X	X		X	X
Hepatic failure	X		X	X	X
Dermatitis/rash	X	X	X	X	X
Serum sickness	X	X	X	X	X
Pancreatitis	X			X	X

CBZ = carbamazepine; ETX = ethosuximide;  
PB = phenobarbital; PHT = phenytoin; VPA = valproate

Pellock J. *Epilepsia*. 1994.

## Idiosyncratic Reactions: Newer AEDs

Reaction	FBM	GBP	LTG	TPM	TGB	ZNS	LEV	OXC
Agranulocytosis	X							
Stevens-Johnson			X			X		
Aplastic anemia	X							
Hepatic failure	X							
Dermatitis/rash	X	X	X	X	X	X	X	X
Serum sickness								
Pancreatitis								

FBM = felbamate; GBP = gabapentin; LTG = lamotrigine;  
TPM = topiramate; TGB = tiagabine; OXC = oxcarbazepine;  
ZNS = zonisamide; LEV = levetiracetam

Glauser TA. *Epilepsia*. 2000.

	VPA	CBZ/OXC	TOP	LEV	LAM
	Depakine	Tegretol Trileptal	Topamax	Keppra	Lamictal
dosage	25	20	5	30	5-10
Indication	P + G	P	P + G	P + G	P + G
Interactions	+/-	+	+/-	-	++
Aggravation	-	+	-	-	+/-
Cognitive Side effects	+/-	+/-	+	-	-
Frequent Adverse effects	Behaviour Tremor  Liver Bone	Headache Hyponatremie Ataxia Psychosis	Kidney Glaucoma Anhidrosis cognition	sleepiness behaviour	Rash



## **Na- Valproate (Depakine)**

- **Indicaties : generaliseerd + partieel / status epilepticus**
- **Dosage : 20-30 mg/kg/dag**
- **Titratie : 2-4 weken**
- **Contraindicaties : Leverziektes / metabole ziektes**  
**cave zuigelingen**
- **Bijwerkingen : tremor, gewicht, gedrag, osteoporose,**  
**stolling, endocrien**



# Carbamazepine / Oxcarbazepine

## (Tegretol, Trileptal)

- **Indicaties : partiële epilepsie**  
**'narrow spectrum'**
- **dosage : 15-20 mg/kg/dag**
- **Titratie : 2-4 weeks**
- **Contra-indicaties**
- **Bijwerkingen : gedrag/psychose, hyponatremie,  
hoofdpijn, ataxie**
  
- **! Inductor + auto-inductor**



## Topiramate (Topamax)

- **Indicaties : partieel en gegeneraliseerd breed spectrum**
- **dosage : 5-9 mg/kg/dag**
- **Titratie : 2-4 weken**
- **Contra indicaties : nierinsufficiëntie**
- **Bijwerkingen : nierstenen, paresthesieën, cognitieve bijwerkingen**



## Lamotrigine (Lamictal)

- **Indicaties :**                    **partieel + gegeneraliseerd  
breed spectrum AED**
- **Dosage :**                        **5-15mg/kg/day**
- **!!! Titratie**
- **Contra-indicaties :**
- **Bijwerkingen : rash, toename myocloniën**



## Lamotrigine : titration

- + valproate
  - 0.1 mg/kg/dag week 1
  - 0.3 mg/kg/dag week 2
  - 0.5 mg/kg/dag week 3
  - eiddosis: 1 - 5 mg/kg/dag
  
- + carbamazepine
  - 1- 2 mg/kg/dag week 1 and 2
  - 5 mg/kg/dag week 3 and 4
  - eiddosis : 5 -15 mg/kg/dag



## Levetiracetam (Keppra)

- **Indicaties : partieel en gegeneraliseerd breed spectrum**
- **Dosage : 10-50 mg/kg/day (30mg/kg/d)**
- **Titratie : 2-4 weken**
- **! Geen interacties**
- **Contra-indicaties :**
- **Bijwerkingen : gedrag, slaperigheid**



## Vigabatrin (Sabril)

- **Indicatie : West syndroom, infantiele spasmen**
- **Dosage : 50 - 150 mg/kg/dag**
- **Titratie : snel**
- **Bijwerkingen : hypotonie, visueel veld defecten**



## Ethosuximide (Zarontin)

- **Indicaties :** absence aanvallen  
(myoclonie aanvallen – GTC)
- **dosage :** 20 mg/kg/day (alleen siroop)
- **Titratie :** 2-4 weeks
- **Bijwerkingen :** gastro-intestinaal



- **Trage opbouw en afbouw**
- **BID betere compliantie**
- **Oppassen met voorgeschreven capsules/siroop TID**
- **Associatie met dagelijkse activiteiten (maaltijden) beter dan strikt tijdschema**
- **Medicatie box verhoogt compliantie**
- **Extra dosis bij 1 x vergeten / braken <30 minuten**
- **Interacties met andere medicatie (maagbescherming)**
- **Bloedspiegels geen goede leidraad voor therapie**





**Met dank aan**

**Birgit Verhelle  
An Verstrepen  
Jan Vervisch  
Ivan Myatchin**