

# Update on clinical recommendations for epilepsy in TSC

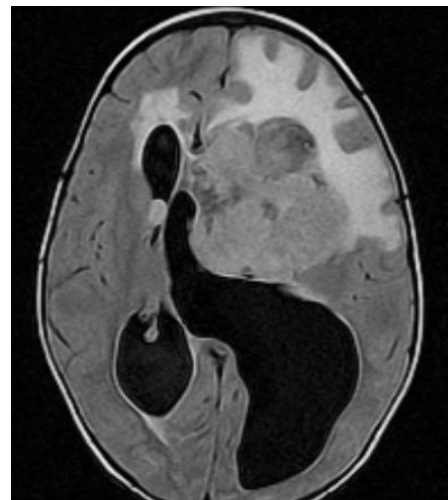
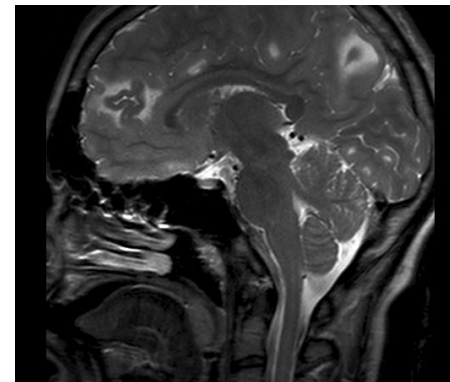
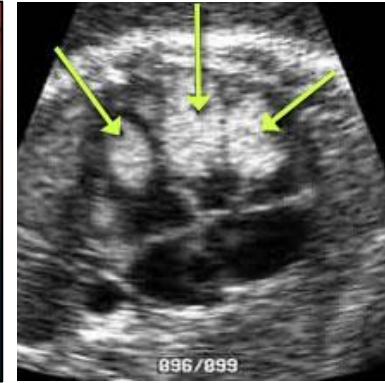
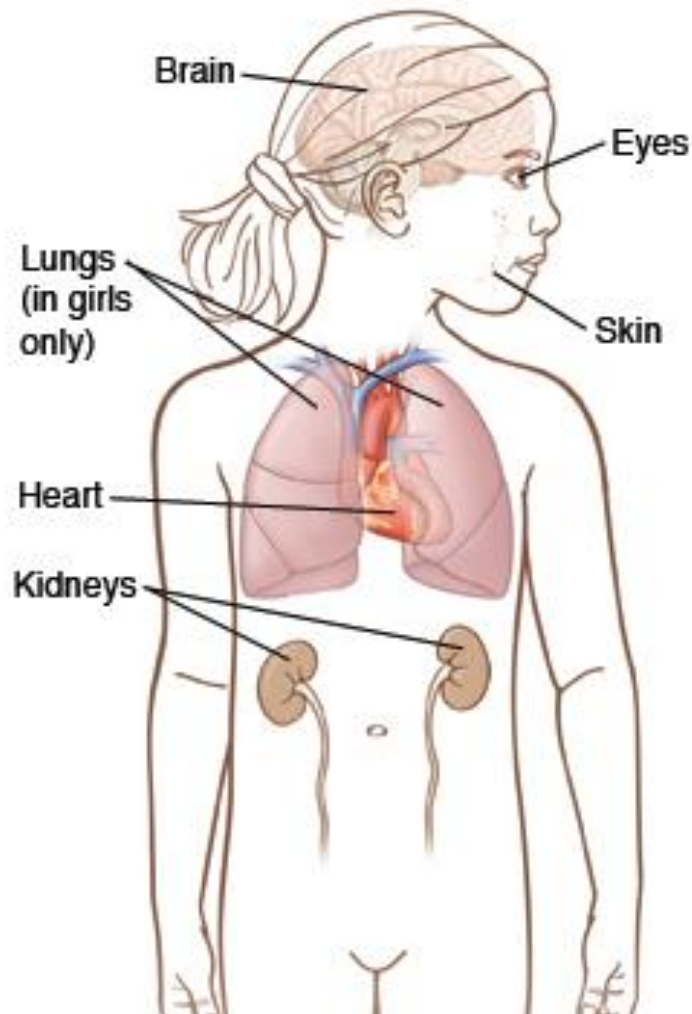
**Liesbeth De Waele, MD, PhD**

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19 October 2018

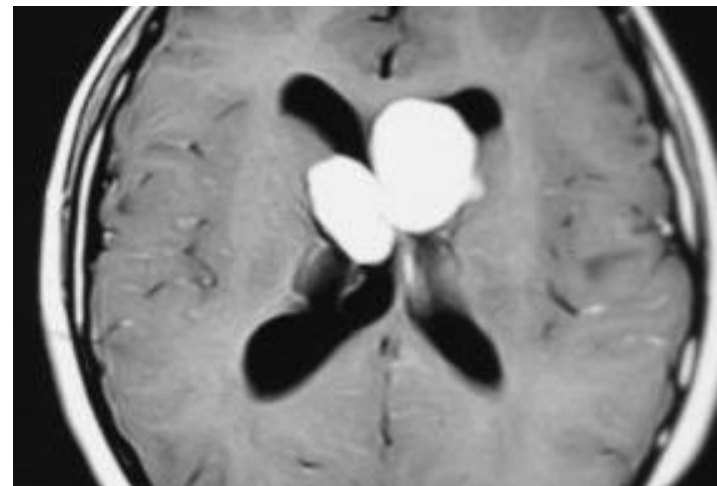
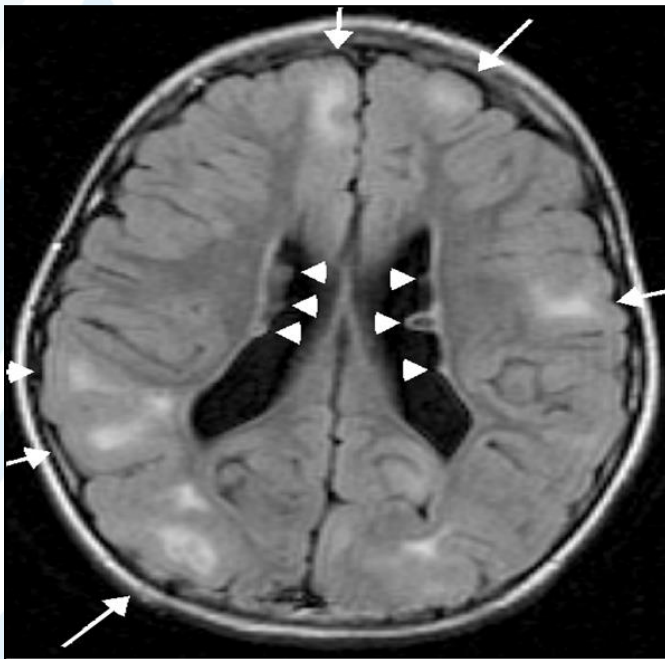
# Tuberous Sclerosis Complex (TSC)

benign tumours (hamartomas)  
in multiple organs

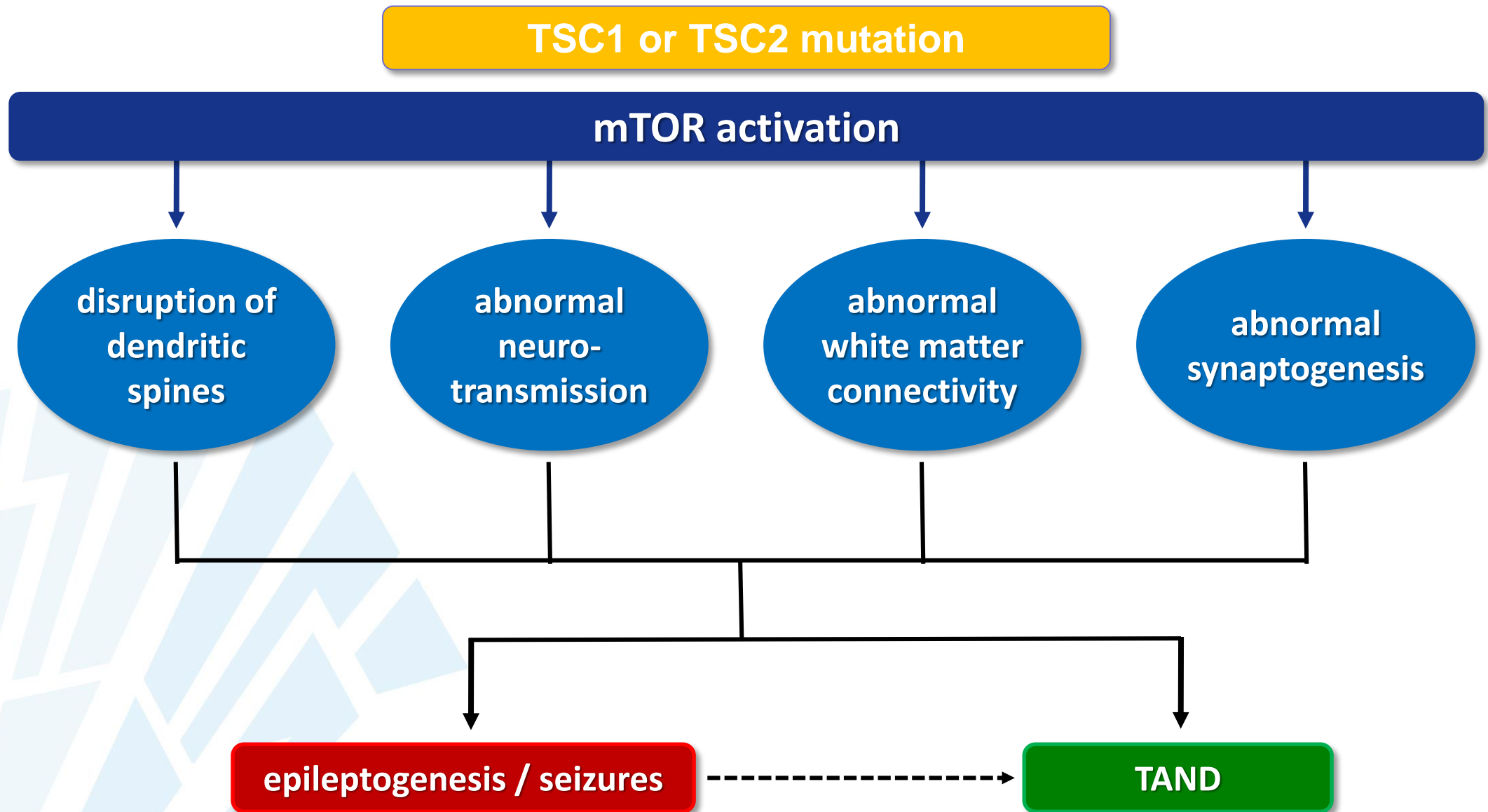


# Central nervous system manifestations in TSC

- cortical tubers (80-90%)
- cerebral white matter radial migration lines (20%)
- SEN: subependymal nodules (80%)
- SEGA: subependymal giant cell astrocytoma (5-20%)

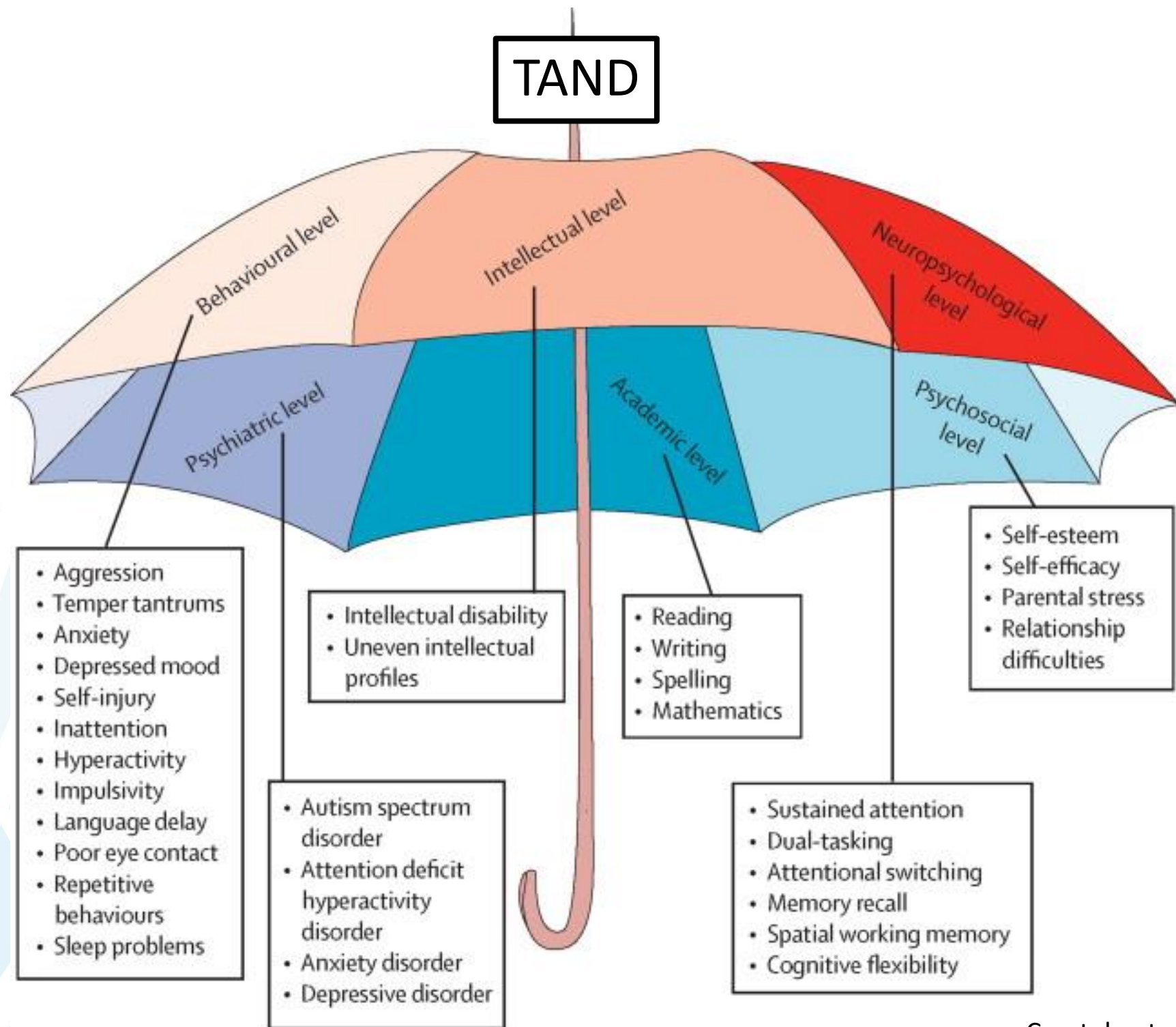


# Central nervous system manifestations in TSC



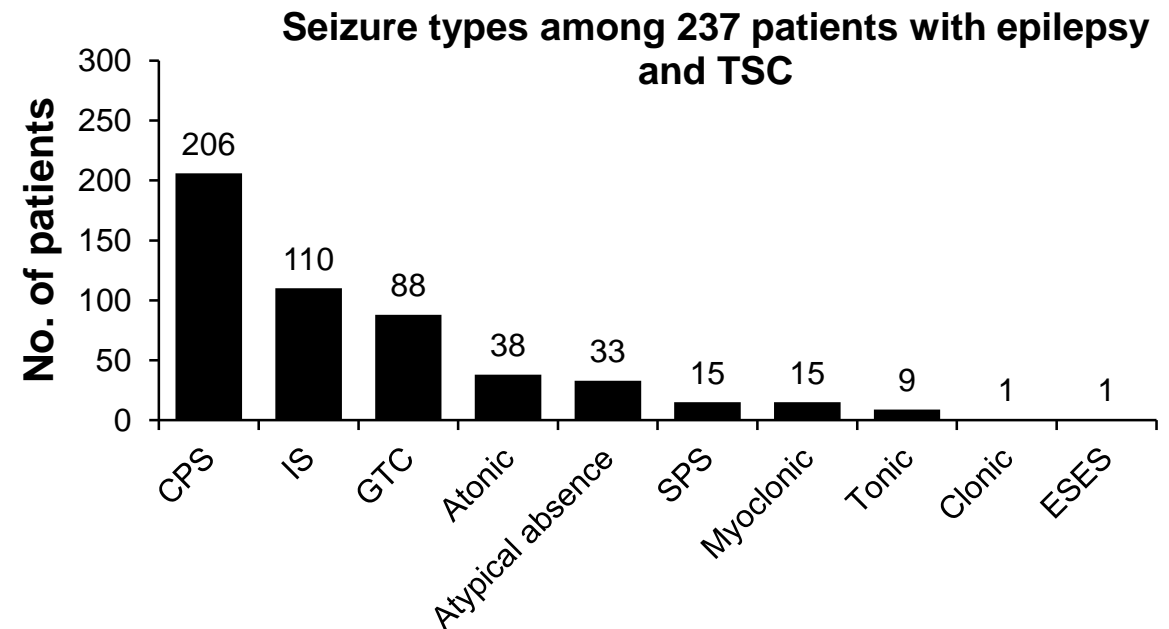
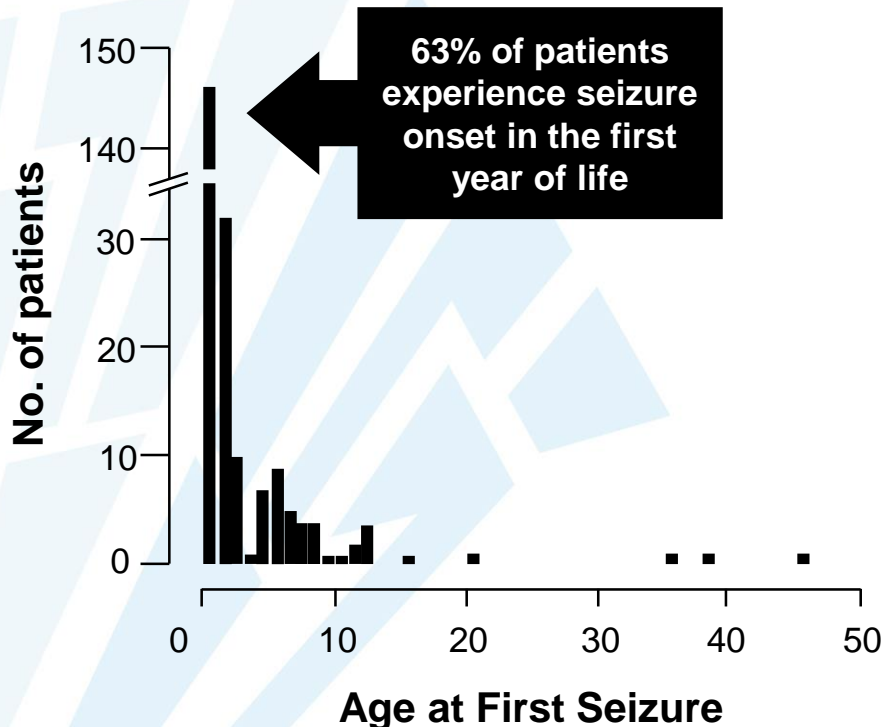


# TAND



# Epilepsy in TSC

- most common neurological symptom in TSC: 75-90% of patients
- onset most often in the first year of life
- focal seizures are most common seizure type
- >60% refractory seizures

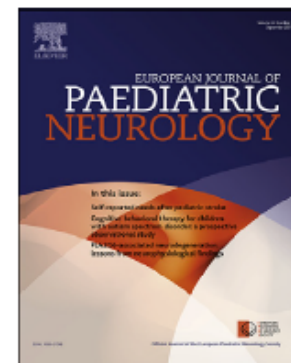


# Updated clinical recommendations

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 22 (2018) 738–748



Official Journal of the European Paediatric Neurology Society



## Review article

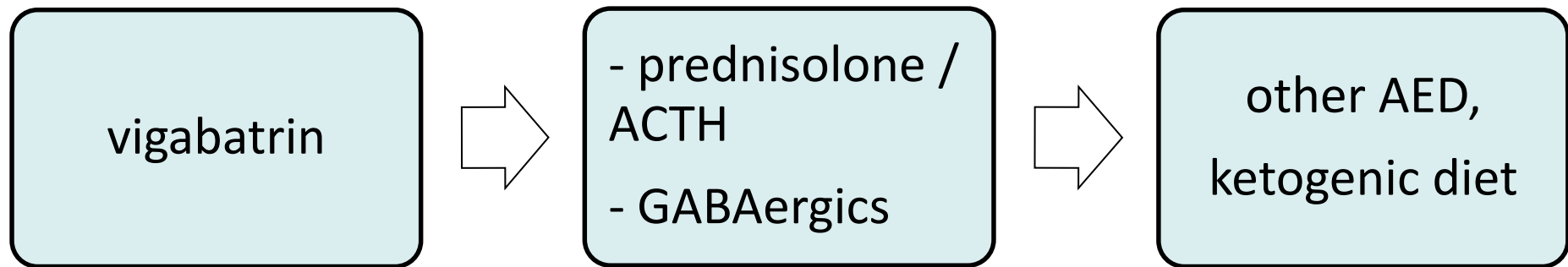
# Management of epilepsy associated with tuberous sclerosis complex: Updated clinical recommendations



Paolo Curatolo <sup>a,\*</sup>, Rima Nabhout <sup>b</sup>, Lieven Lagae <sup>c</sup>, Eleonora Aronica <sup>d,e</sup>,  
José Carlos Ferreira <sup>f</sup>, Martha Feucht <sup>g</sup>, Christoph Hertzberg <sup>h</sup>,  
Anna C. Jansen <sup>i</sup>, Floor Jansen <sup>j</sup>, Katarzyna Kotulska <sup>k</sup>, Romina Moavero <sup>a,l</sup>,  
Finbar O'Callaghan <sup>m</sup>, Antigone Papavasiliou <sup>n</sup>, Michal Tzadok <sup>o</sup>,  
Sergiusz Jóźwiak <sup>p</sup>

# Anti-epileptic drugs for epilepsy in TSC

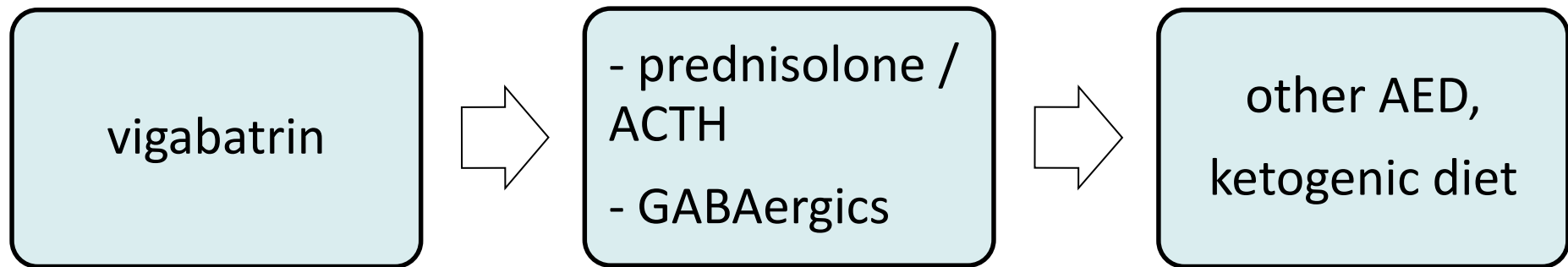
- infantile spasms



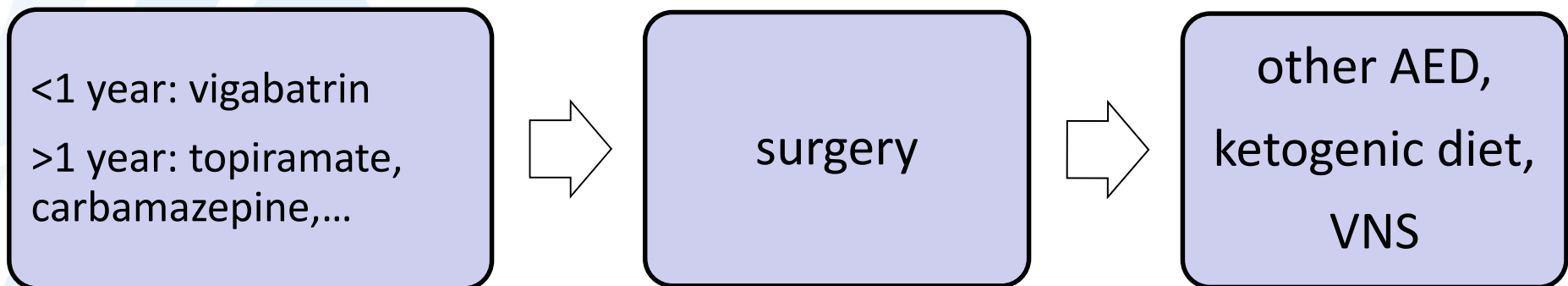


# Anti-epileptic drugs for epilepsy in TSC

- infantile spasms



- focal seizures

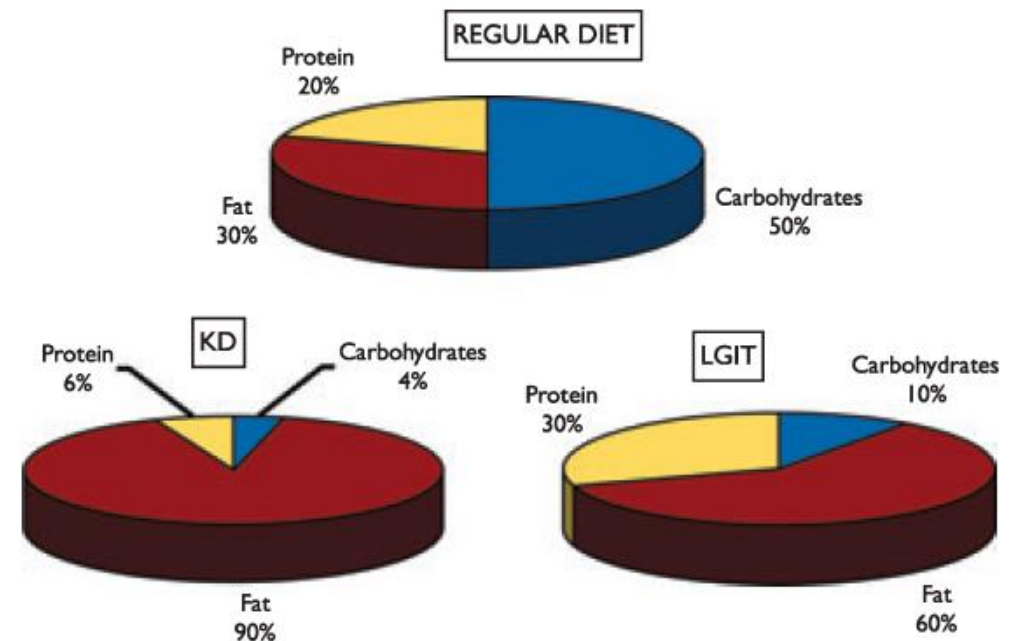


# Surgery for epilepsy in TSC

- currently underutilized in TSC-associated refractory seizures
- usually restricted to focal seizures and single EEG focus, but should also be considered when bilateral or multifocal lesions
- after failure of 2 AEDs
- early comprehensive presurgical evaluation
- early surgery significantly increases probability to be seizure-free (55-60%)

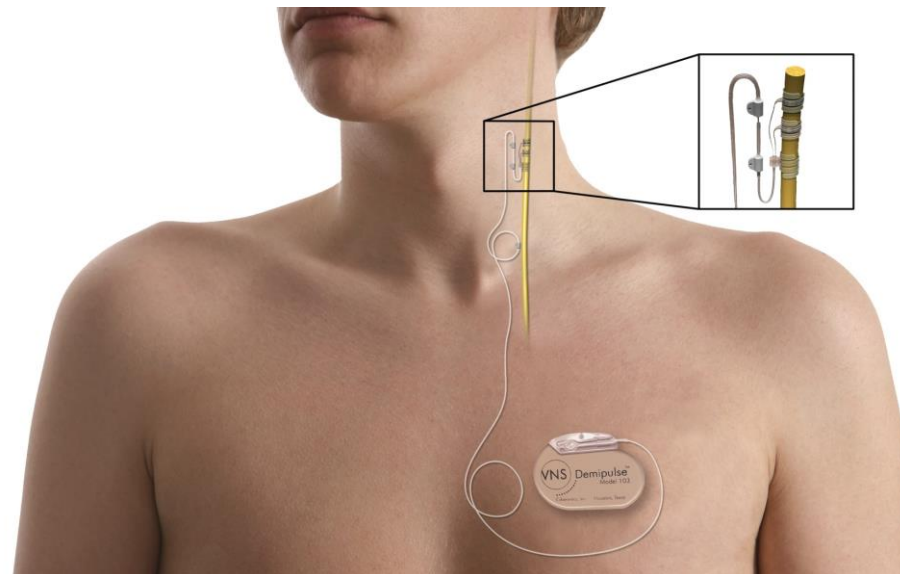
# Ketogenic diet for epilepsy in TSC

- should be considered
  - for patients who are not surgical candidates (also in early infancy/childhood)
  - when surgery failed
  - when multifocal seizure onset
- difficult compliance after infancy



# VNS for epilepsy in TSC

- may be a first option when ketogenic diet is not acceptable, or may be combined with ketogenic diet
- data are limited, but significant reduction in seizure frequency in about 50% of patients was reported
- almost no patients become seizure-free



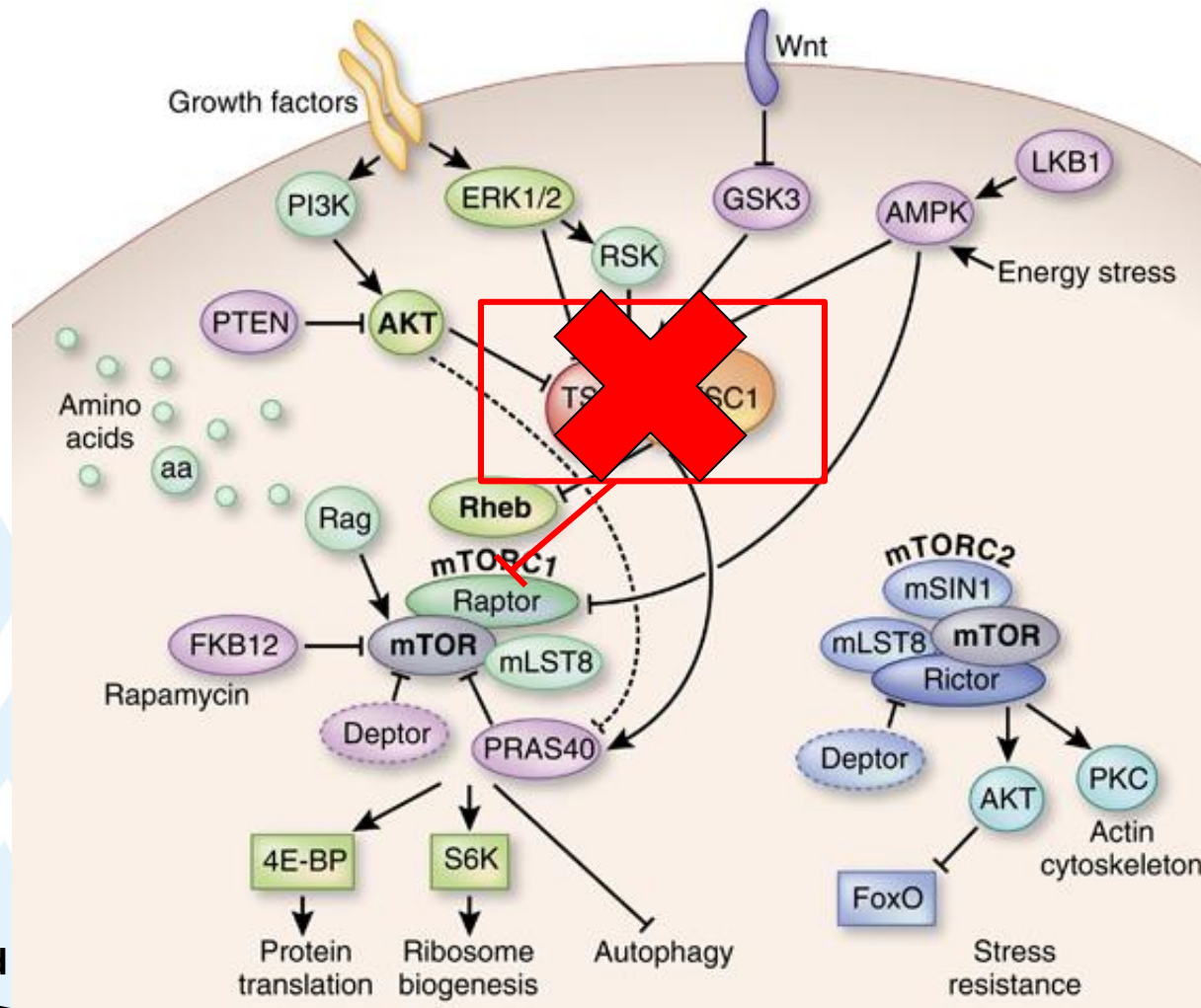
# Cannabidiol (CBD) for epilepsy in TSC

- clinical trial results pending, mainly anecdotal reports
- limited experience in Europe
- mechanism of action remains unclear





# mTOR pathway



cell growth and proliferation

SEGA, AML

angiogenesis and lymphangiogenesis  
AML, LAM

Cell growth and metabolism

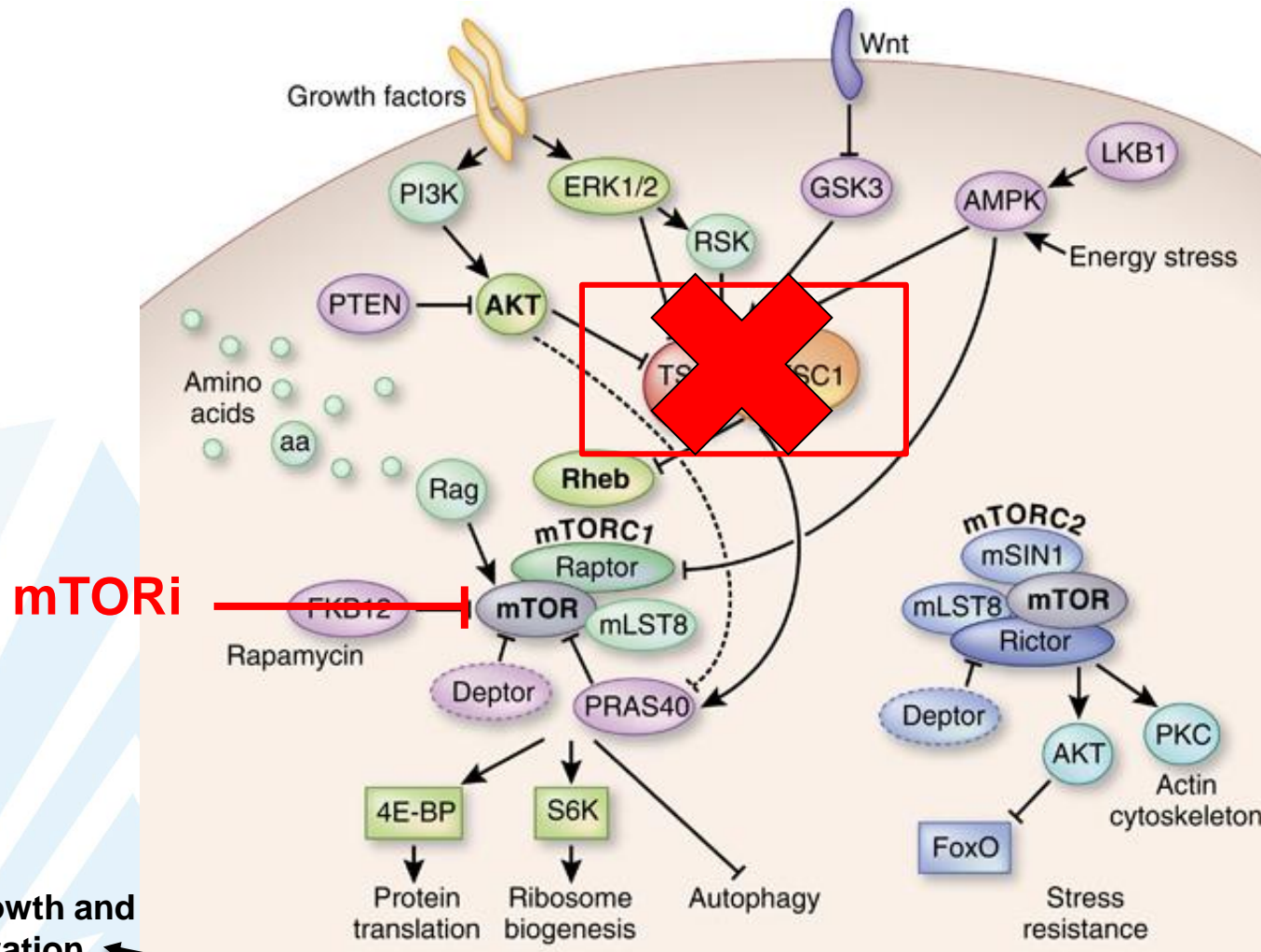
cell metabolism and glucose uptake

cell orientation and migration

neuronal dysfunction

tubers, cortical dysplasia

# mTOR pathway



**mTORi**

cell growth and proliferation

**SEGA, AML**

**AML, LAM** angiogenesis and lymphangiogenesis

Cell growth and metabolism

cell metabolism and glucose uptake

cell orientation and migration

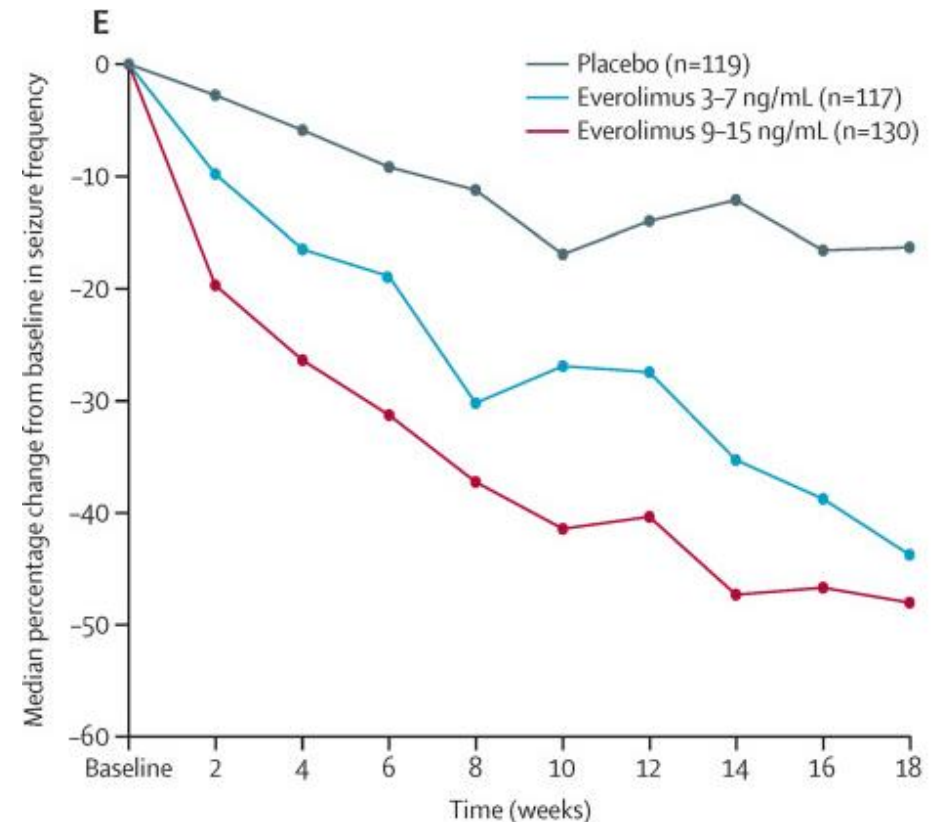
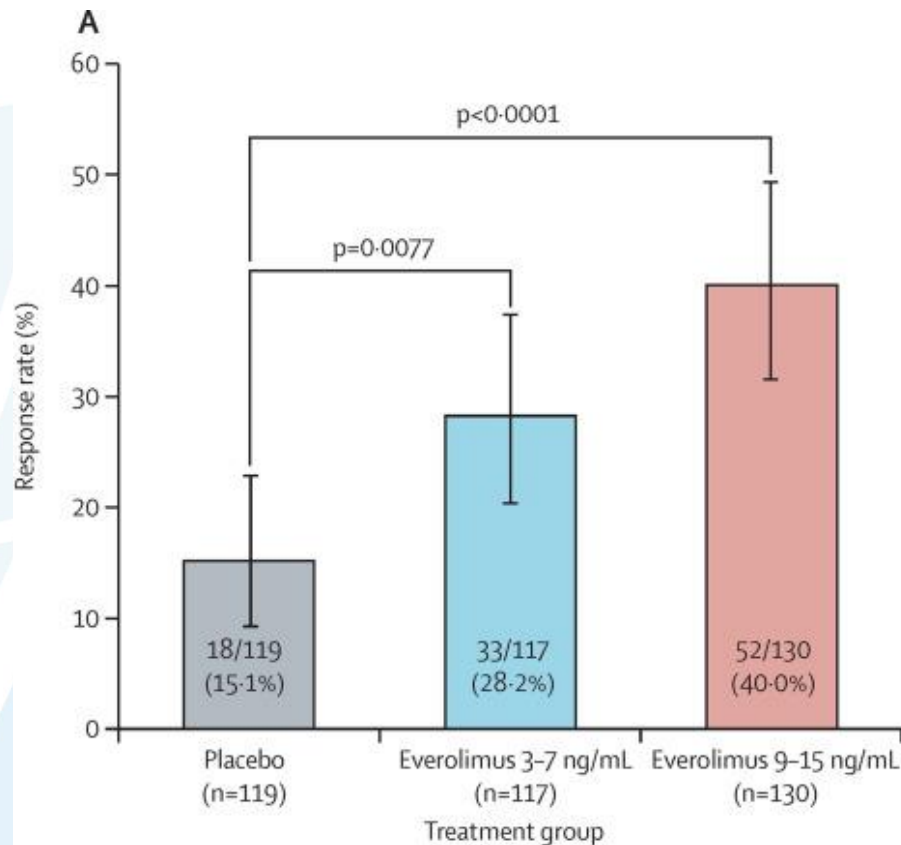
**tubers, cortical dysplasia**

**neuronal dysfunction**

# mTOR inhibitors for epilepsy in TSC

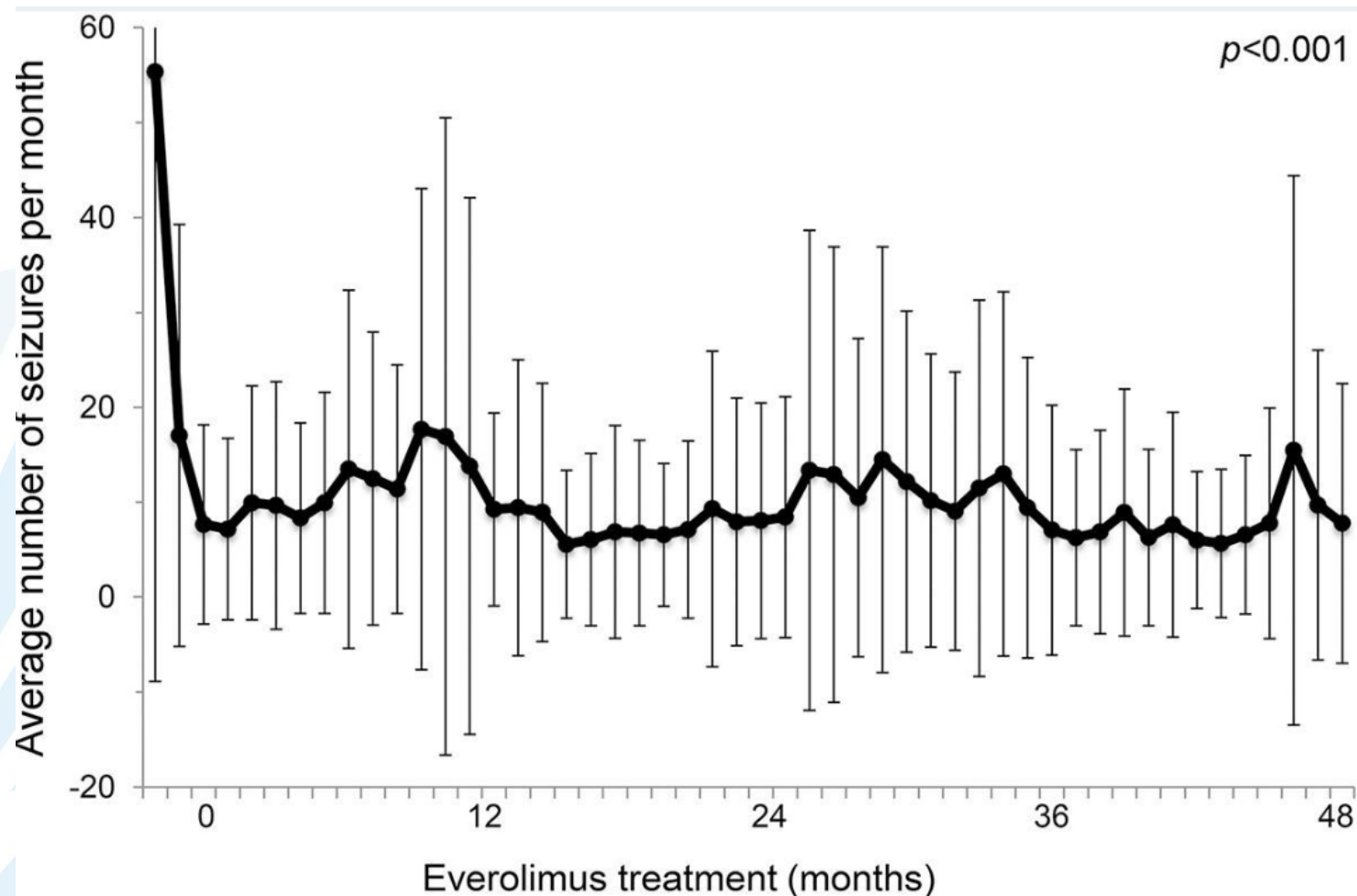
Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis  
(EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study

Jacqueline A French, John A Lawson, Zuhair Yapici, Hiroko Ikeda, Tilman Polster, Rima Nabbout, Paolo Curatolo, Petrus J de Vries, Dennis J Dlugos, Noah Berkowitz, Maurizio Voi, Severine Peyrard, Diana Pelov, David N Franz



# mTOR inhibitors for epilepsy in TSC

- EXIST-3 extension phase demonstrated sustained efficacy

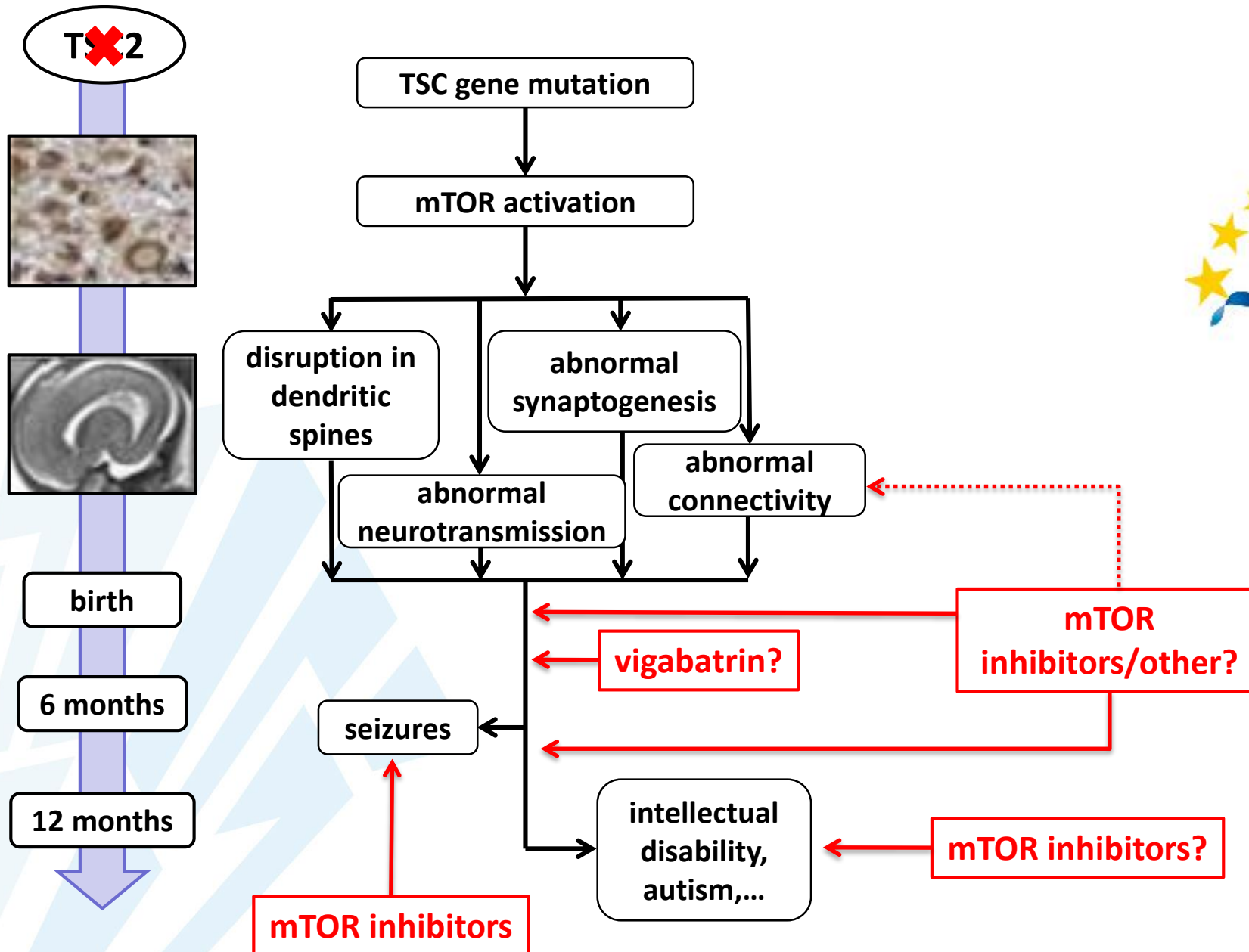


# mTOR inhibitors for epilepsy in TSC

- EXIST-3 extension phase demonstrated sustained efficacy
- long-term treatment was safe and well tolerated
- approval by EMA DEC 2016 for refractory partial-onset seizures (with or without generalisation) in TSC patients >2 years
- should be considered as add-on therapy when seizures are refractory to 2 AEDs
- multisystemic treatment!
- earlier treatment?



# Epileptogenesis in TSC



# Take home messages

- need for early diagnosis of epilepsy as early treatment improves outcome!
  - education of parents (<http://infantielespasmen.be/>)
  - early EEG monitoring (?)
- vigabatrin may be considered presymptomatically when subclinical epileptiform discharges on EEG
- early surgical evaluation
- adjunctive everolimus for refractory seizures >2 years
- earlier introduction of mTOR inhibitors?





# Clinical manifestations in TSC

