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Understanding Lennox-Gastaut Syndrome (LGS): Recent Treatment Approaches, Management, and Care Coordination

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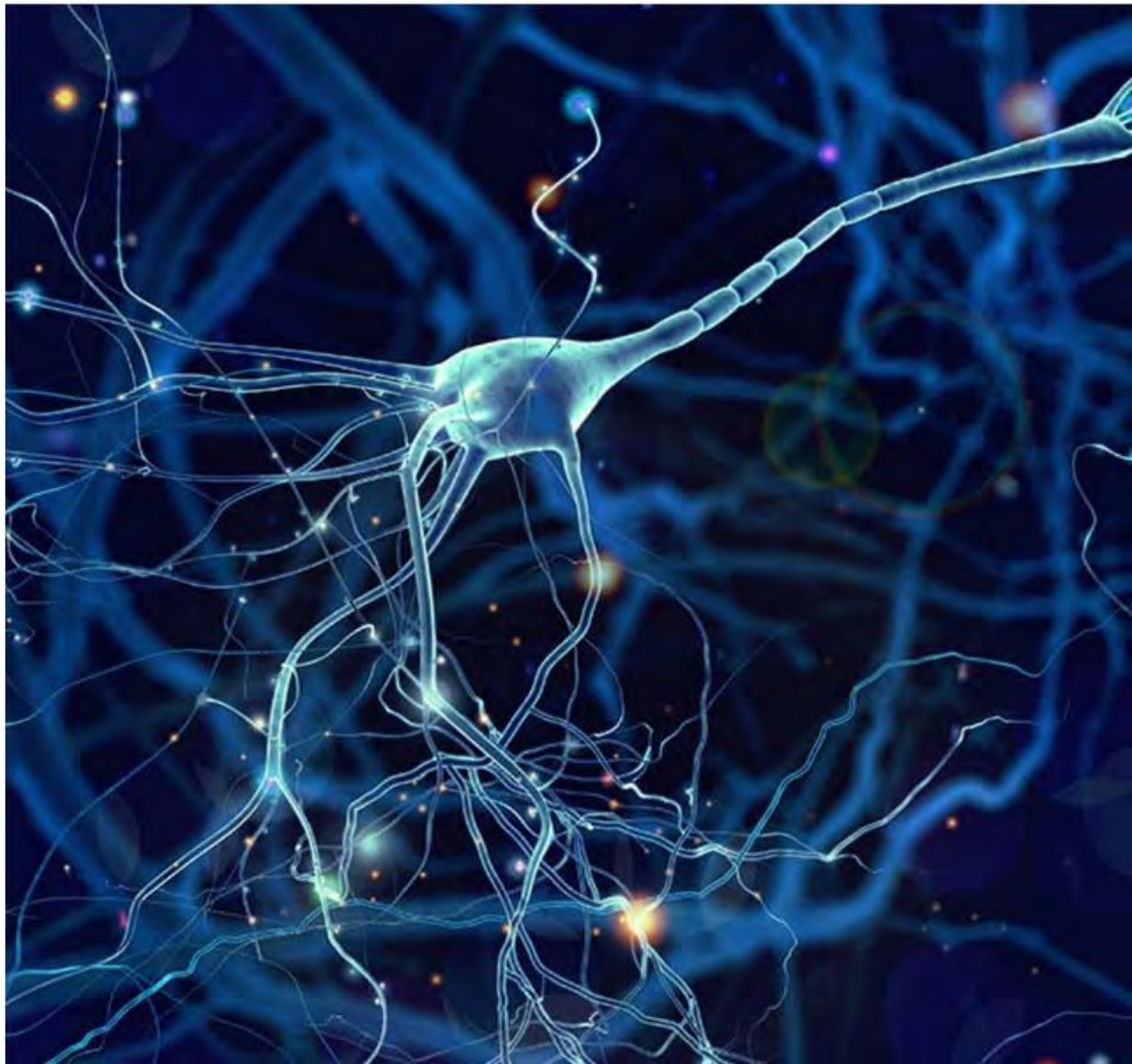

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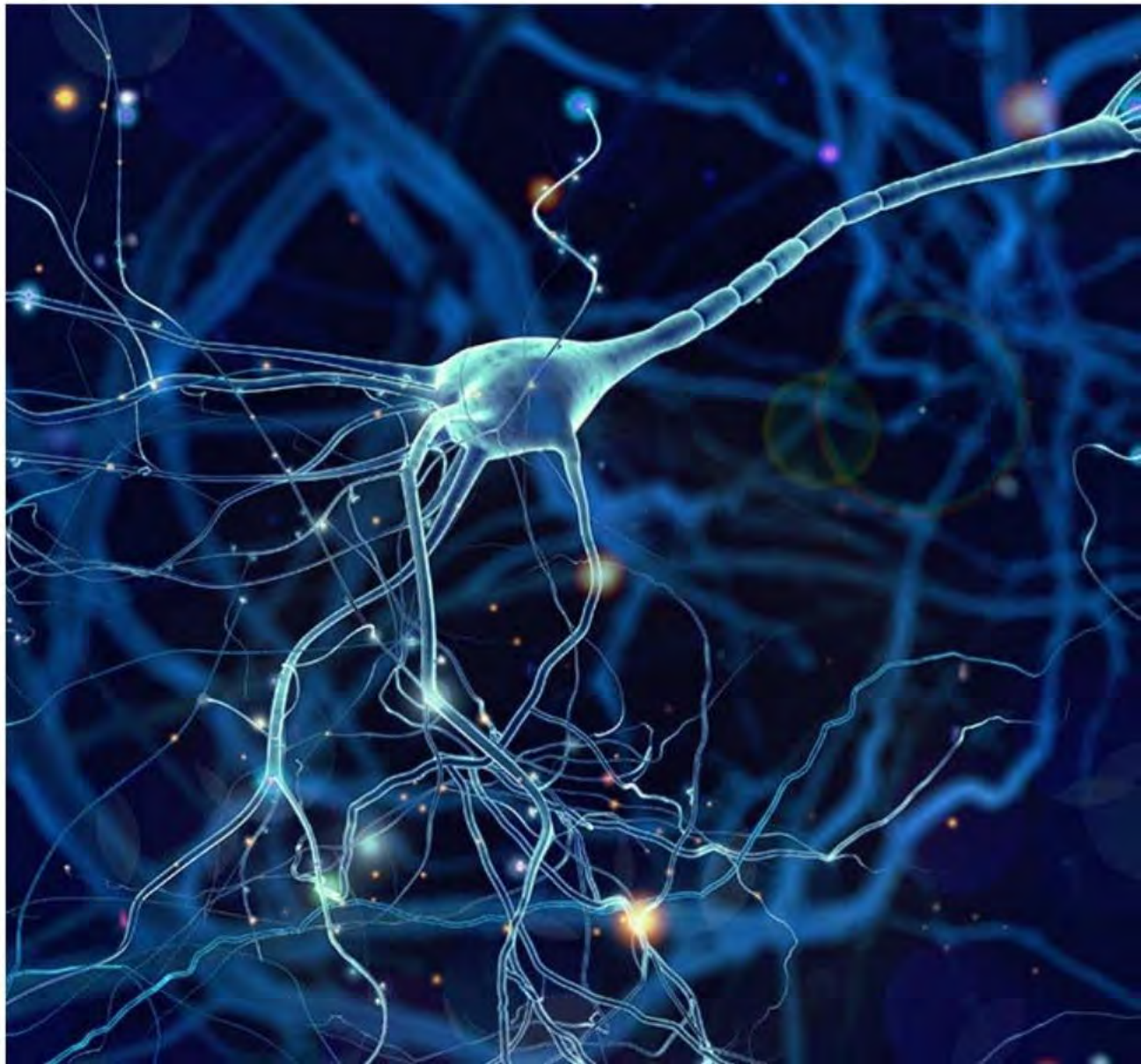
Understanding LGS: Recent Treatment Approaches and Management



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Objectives

- Define treatment goals
- Review treatment options
- Ideas for treatment selection

Definition of Lennox-Gastaut syndrome

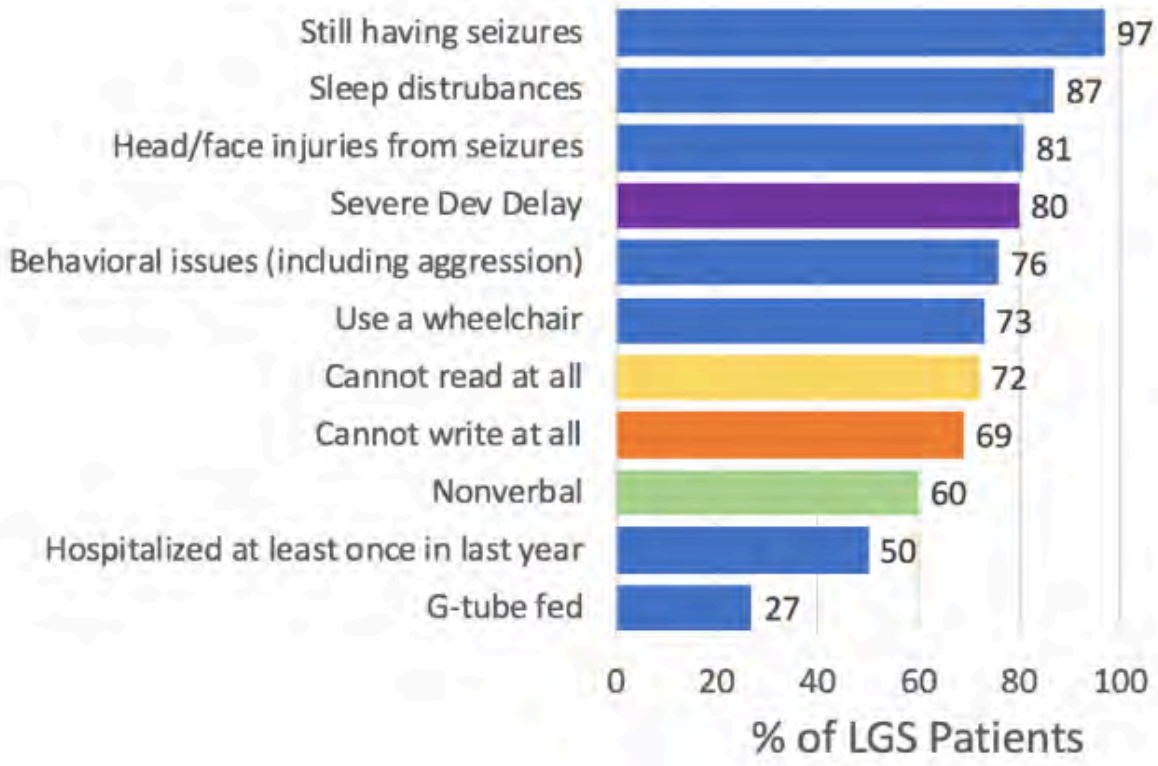
- 1989 ILAE – childhood onset epilepsy with most common seizures being tonic and atypical absence, followed by myoclonic, tonic/atonic “drops”, generalized tonic-clonic, and focal seizures
- Cognitive impairment is nearly universal
- EEG shows <2.5Hz spike-and-wave pattern
- Classic “triad” though not all patients have all core seizure types

Camfield, PR, Epilepsia, 52(Suppl. 5):3–9, 2011
www.lgsfoundation.org

ILAE updated definition (2021)

- Multiple types of drug-resistant seizures with onset *prior to 18 years* (one must be tonic seizures)
- Cognitive impairment
- Diffuse slow spike-wave and generalized paroxysmal fast activity

Major issues reported by LGS caregivers



Caregiver Priorities:

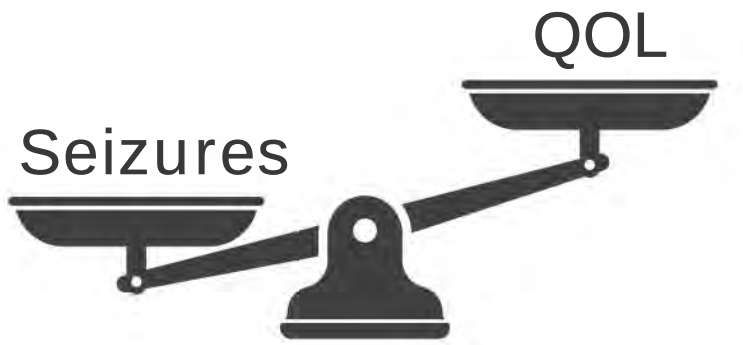
1. Seizures and safety
2. Delay/ID, especially communication
3. Behavior, especially aggression
4. Mobility and physical care issues
5. Sleep
6. Costs/Access to care
7. Social Isolation

n=416

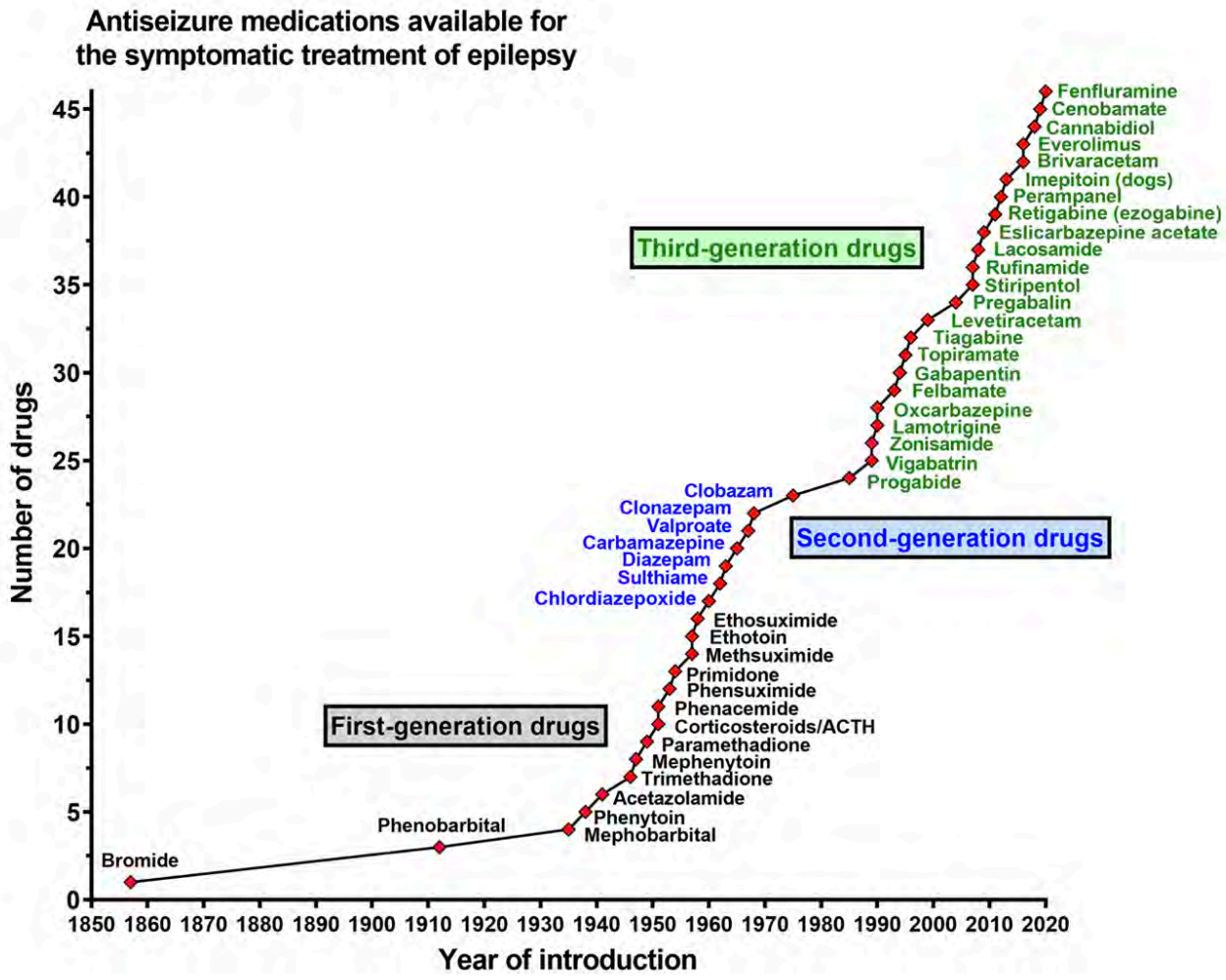
LGS Foundation Caregiver Survey

No seizures, no side effects

- We are getting closer to better side effects, but little change in response rates ...
- Perhaps improvement in side effects or at least more medications to choose from when thinking about side effects
- More realistic goal for my patients – the least amount of seizures possible with the best quality of life possible



So many new medications from which to choose!



Löscher and Klein, CNS Drugs 2021

Response to medication, unchanged

Table 2. Rates of 1-Year Seizure Freedom With Successive Antiepileptic Drug Regimens

Successive Antiepilepsy Drug Regimens	Total Patients Trying These Regimens, No.	Seizure Freedom			
		Total, No.	% of Patients Achieving Seizure Freedom With AED Regimen	% of the Total Achieving Seizure Freedom (n = 1144)	% of the Total Study Cohort (n = 1795)
First	1795	820	45.7	71.7	45.7
Second	742	208	28.0	18.2	11.6
Third	330	78	23.6	6.82	4.35
Fourth	140	21	15.0	1.84	1.17
Fifth	71	10	14.1	0.87	0.56
Sixth	43	6	14.0	0.52	0.33
Seventh	15	1	6.67	0.09	0.06
Eighth	9	0	0	0	0
Ninth	5	0	0	0	0
Tenth	2	0	0	0	0
Eleventh	1	0	0	0	0
Total	1795	1144	NA	100.04[a]	63.7

TABLE 2. SUCCESS OF ANTIEPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

VARIABLE	NO. (%)
Response to first drug	222 (47)
Seizure-free during continued therapy with first drug	207 (44)
Remained seizure-free after discontinuation of first drug	15 (3)
Response to second drug	61 (13)
Seizure-free during monotherapy with second drug	41 (9)
Remained seizure-free after discontinuation of second drug	20 (4)
Response to third drug or multiple drugs	18 (4)
Seizure-free during monotherapy with third drug	6 (1)
Seizure-free during therapy with two drugs	12 (3)
Total	301 (64)

Chen et al, JAMA neurology 2018, Kwan and Brodie, NEJM 2000

Phase 3 RCT summary

ASM	Overall Percent Reduction in Drop seizures	Placebo	50% responder rate	Other
Felbamate (1993)	34%	9%		10% sz free
Lamotrigine (1997)	32%	9%	33%	GTC reduction 46%
Topiramate (1999)	26%	15%	33%	
Rufinamide (2008)	42%	1%	47%	
Clobazam (2011)	41-68%	59-78%		7-24% sz free
Cannabidiol (2018)	44%	21%	36-39%	11-25% with 75% reduction
Fenfluramine (2020)	26%	7%	25%	GTC reduction 45-58%

Verrotti A, et al. Seizure: European J of Epilepsy, Oct 2018

Treatments not studied

Valproate
ACTH
Corpus callosotomy
Zonisamide
Levetiracetam
Ketogenic diet
VNS
Surgical resection

Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomised, double-blind, placebo-controlled phase 3 trial

*Elizabeth A Thiele, Eric D Marsh, Jacqueline A French, Maria Mazurkiewicz-Beldzinska, Selim R Benbadis, Charuta Joshi, Paul D Lyons, Adam Taylor, Claire Roberts, Kenneth Sommerville, on behalf of the GWPCARE4 Study Group**

N = 171

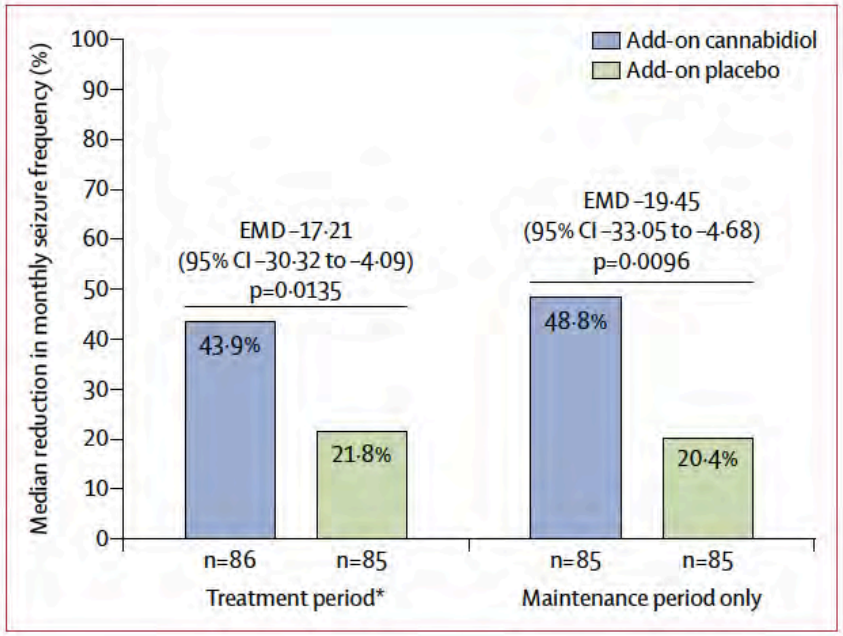
20 mg/kg/d CBD compared to placebo

Inclusion:

- Lennox-Gastaut syndrome (slow spike and wave, multiple seizure types)
- >2 “drop seizures” per week
- Stable meds for 4 weeks

Results:

- CBD 71.4 → 31.4 median seizures/month
- Placebo 74.7 → 56.3 median seizures/month



Fenfluramine in patients with LGS

Randomized, double-blind, PBO-controlled, phase III trial

n = 263

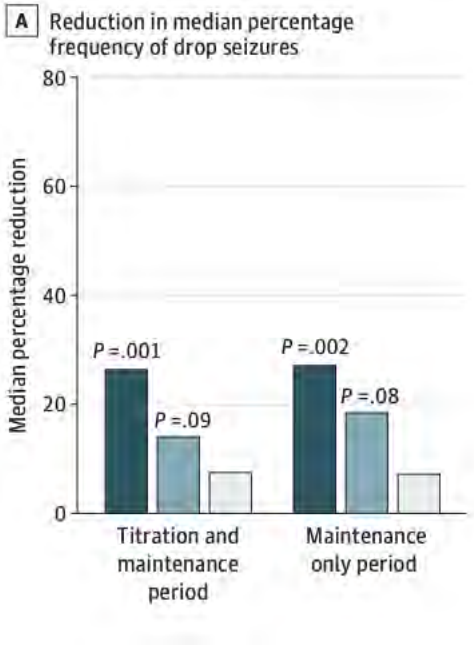
0.2 mg/kg/day,
0.7 mg/kg/day, placebo

Inclusion:

- LGS (slow spike and wave, multiple seizure types)
- >2 “drop seizures” per week
- Stable medications for 4 weeks

Results:

0.7 mg/kg/day vs placebo -19.9% median difference in drop seizures

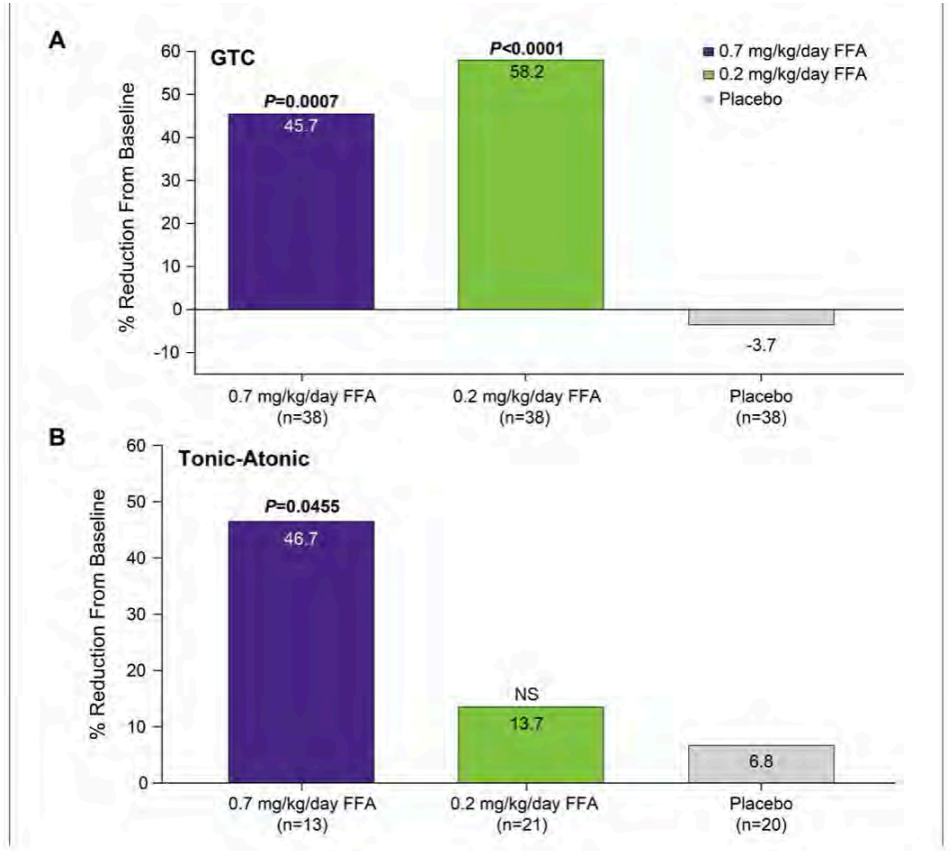


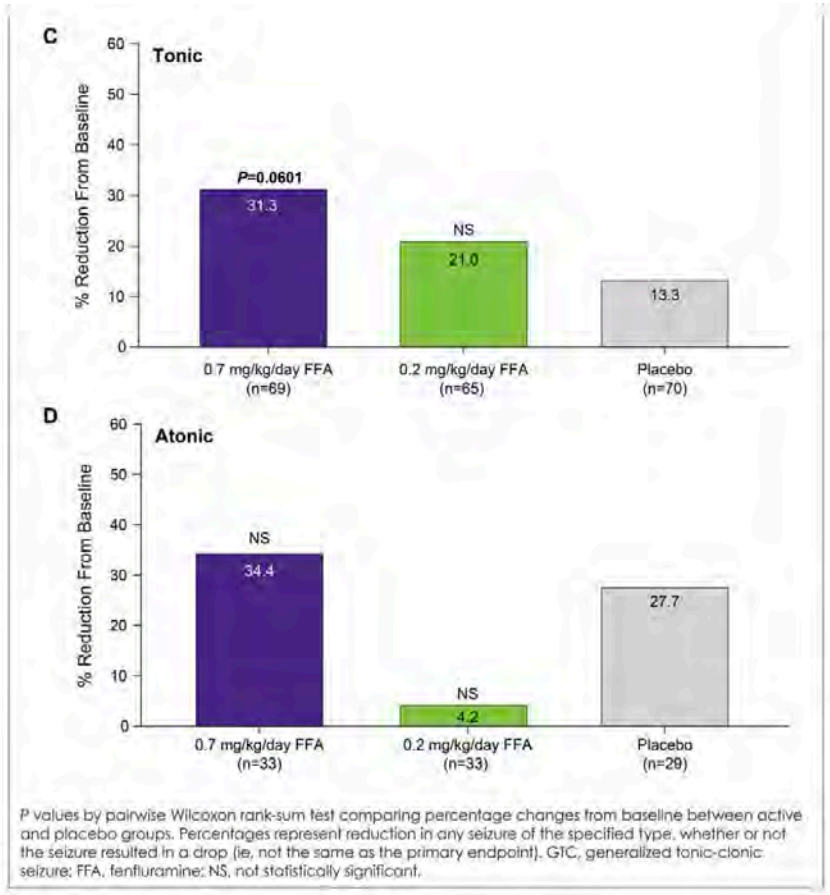
Knupp K. Presented at: American Epilepsy Society Annual Meeting 2020. December 4, 2020; Knupp et al, JAMA Neurology 2022.

Response by seizure type

Median % reduction from baseline

Subgroup Analysis by Seizure Type, Median Percentage Reduction from Baseline





Knupp K et al. *JAMA Neurology*. 2022;79(6):554-564

Solticlestat in Lennox-Gastaut syndrome

n = 88

Max dose of :

- 300 mg/day ≥60 kg
- Titrated dose <60 kg

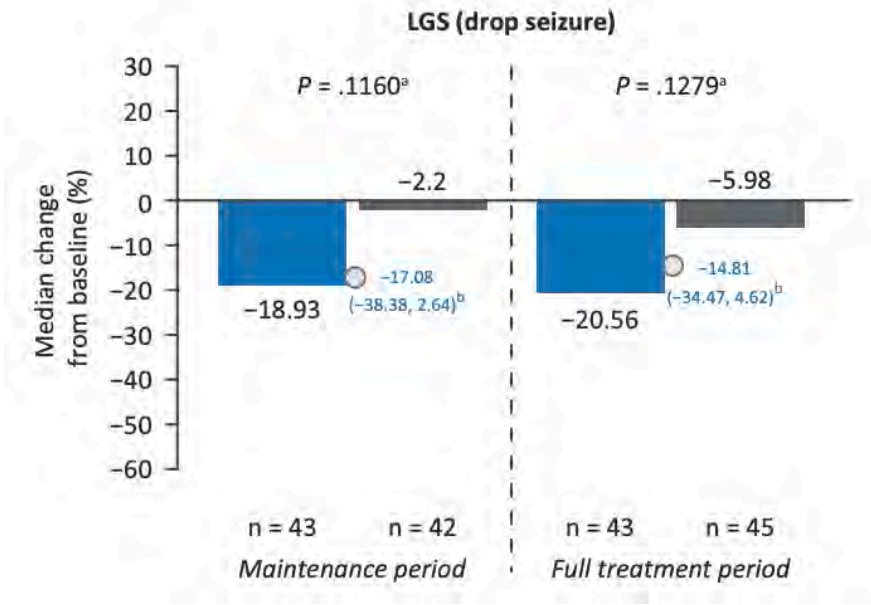
Inclusion:

- Confirmed LGS
- >4 “drop seizures” month
- Stable medications for 4 weeks

Results: (not statistically significant)

Solticlestat 18.3% median reduction in seizures

PCB 2.2% median reduction in seizures



Hahn C et al, Epilepsia 2022

Lorcaserin

- Retrospective review

- 36 patients treated
  - 1 stopped after 3 days due to SE
  - Dravet syndrome = 20
  - LGS = 9
  - Focal epilepsy = 3
  - Generalized epilepsy = 3

- Median reduction of seizures 47.7%
- 2 patients (5.7%) had increased seizures
- At 15 months, 50% were still taking medication

Tolete P et al, Neurology 2018

Treatment recommendations

Treatment Guidelines for Rare, Early-Onset, Treatment-Resistant Epileptic Conditions: A Literature Review on Dravet Syndrome, Lennox-Gastaut Syndrome and CDKL5 Deficiency Disorder

Richard F. Chin[1], Ana Mingorance[2,3], Benjamin Ruban-Fell[4], Isabelle Newell[4], Jenni Evans[5], Kishan Vyas[6], Charlotte Nortvedt[6] and Sam Amin[7]*

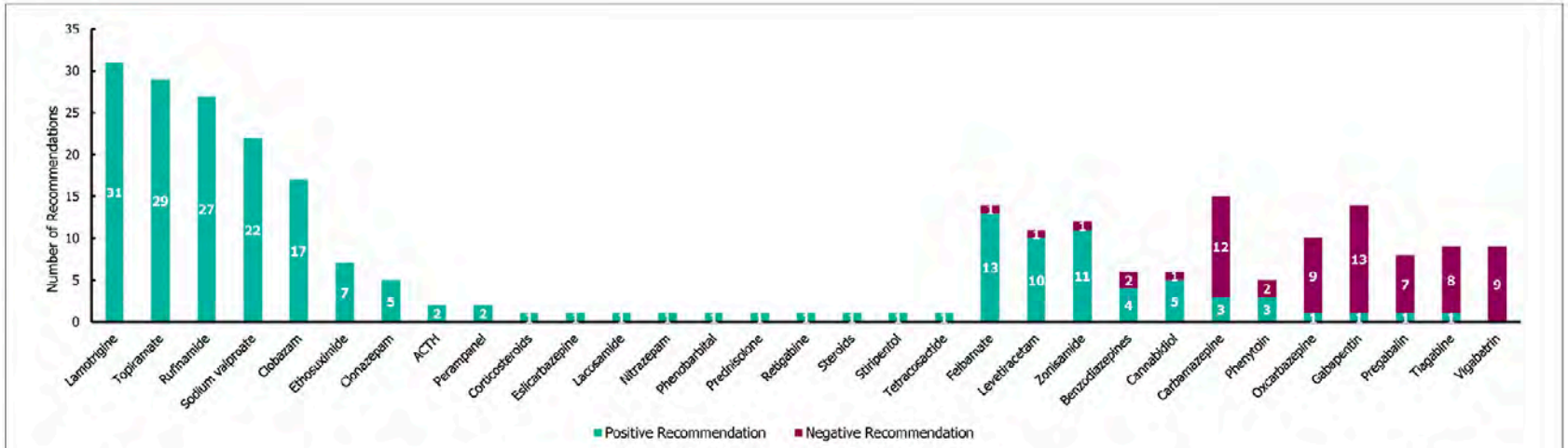


FIGURE 8 | Treatment recommendations for Lennox-Gastaut syndrome. $N = 271$ (205 positive and 66 negative treatment recommendations) from 34 guidelines. Positive recommendation: use of an individual ASM treatment that was recommended for use in a specific indication, irrespective of the line of treatment (e.g., first line) or whether the treatment was adjunctive; negative recommendation: an individual ASM treatment that was highlighted as a potential option by a guideline but whose use was recommended against (for any reason) in a specific indication, irrespective of the line of treatment, or whether the treatment was adjunctive.

Ketogenic diet and VNS

Table 3. Outcome data for LGS children treated with the ketogenic diet using the intent-to-treat analysis[4]

Time point	<50% Seizure reduction	>50% Seizure reduction	90–99% Seizure reduction	Seizure-free
3 months	18 (25%)	53 (75%)	17 (24%)	3 (4%)
6 months	35 (49%)	36 (51%)	15 (21%)	1 (1%)
12 months	40 (56%)	31 (44%)	13 (18%)	1 (1%)

n = 71.
LGS, Lennox-Gastaut syndrome.
Thirteen children (18%) were lost to follow-up and were included in the <50% seizure reduction group after they were lost even though the majority of them had >50% reduction in seizures at their last encounter.
Reprinted with permission from John Wiley and Sons.

Table 4. Recent studies on the effectiveness of vagus nerve stimulation in LGS patients

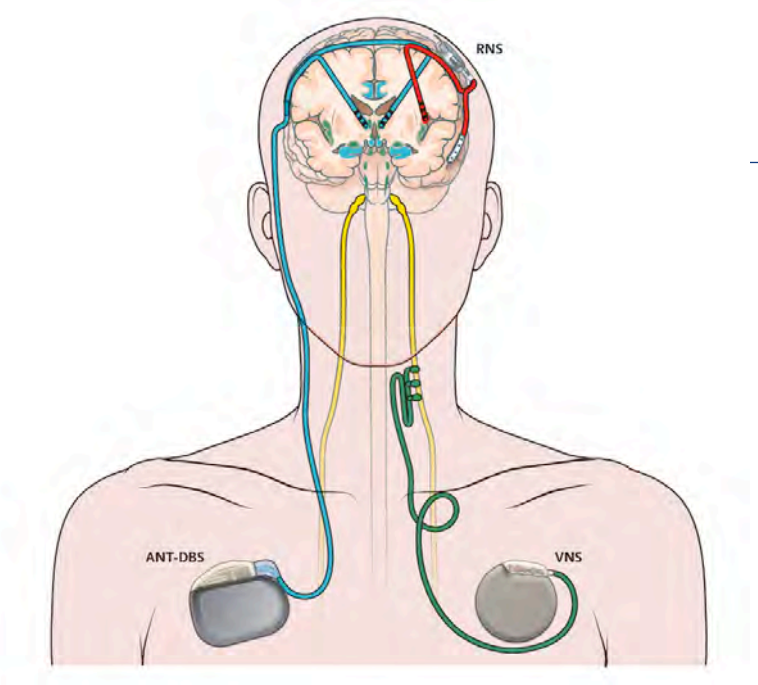
Study	Patients (n)	Treatment length	Patients with >50% reduction in seizures	Other findings
Frost et al.[18]	50	3 months 6 months	56% 58%	QoL improved
Cersosimo et al.[19]	46	Up to 36 months	65%	Improved behavior, cognitive abilities, QoL
Kostov et al.[1]	30	Median of 52 months	60.6% reduction in number of seizures	Best with atonic then tonic seizures; improved alertness in 77% of patients
Shahwan et al.[15]	9	18 months	78%	Tonic seizures most responsive, fewer drop attacks, improved QoL
Aldenkamp et al.[20]	19	24 months	20.6% reduction in seizure frequency	
Majoie et al.[21]	16	6 months	25%	

LGS, Lennox-Gastaut syndrome; QoL, quality of life.

Kossoff EHW et al, Epilepsia 55(Suppl. 4):29–33, 2014

Stimulation

- Reduces seizures, helps with side effects – seizure freedom?
- Increased indications
- Reduction of seizures for our most challenging patients
- Increased personalization for patients, can sense and record
- Can use RNS to record regions of seizure onset in the real world



Ryvlin et al, Lancet Neurology 2021

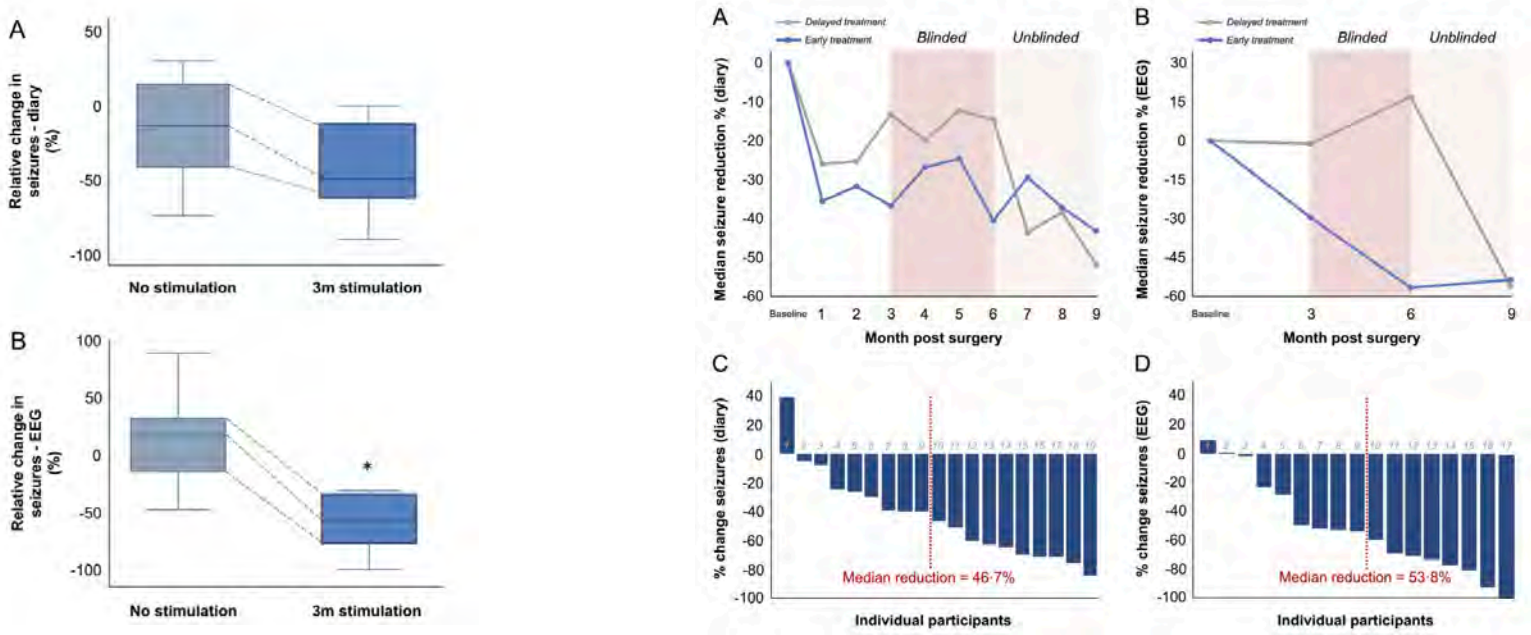
RESEARCH ARTICLE

DBS of Thalamic Centromedian Nucleus for Lennox–Gastaut Syndrome (ESTEL Trial)

Linda J. Dalic, MBBS,[1,2] Aaron E. L. Warren, PhD,[1,3,4] Kristian J. Bulluss, PhD,[5,6,7] Wesley Thevathasan, DPhil,[1,5,8] Annie Roten, BAppSci,[2] Leonid Churilov, PhD,[1] and John S. Archer, PhD[1,2,3,4]

- 20 young adults (ages 17-37 years)
- Bilateral DBS implantation in centromedian nucleus (CM)
- Double-blind/no stimulation design
- Seizures by diary and follow-up 24-hour EEG

ESTEL trial: study findings



59% of the stimulation group had >50% reduction in electrographic seizures compared to none of the controls

Dalic LJ et al. *Ann Neurol.* 2021;91(2):253-267.

Epilepsy surgery

- Several series with great response rates
- Generalized EEG of LGS should not distract from lesional epilepsy
- Focal seizures without a lesion in people with LGS may also benefit from epilepsy surgery
- Every patient should be evaluated for possibility of surgery candidacy

Table 1 Epilepsy Surgery in Pediatric Patients with Lennox Gastaut Syndrome(LGS). Grouped by MRI Finding (Lesional vs Nonlesional), Type(s) of Resection and Associated Engel[4] Outcome.

Reference	# with LGS In the cohort	MRI Finding	Resective Surgery	Engel Outcome
Wylie, et al. 2007[12]	15/50	All lesional	lobar, multilobar, and hemispherotomy (not separated)	67% Engel I
				27% Engel II
				7% Engel IV
Lee, et al. 2010[16]	27/27	23 lesional	hemispherotomy multi-lobar lobar	83.3% Engel I
				60% Engel I
				45.5% Engel I
		4 non-lesional	lobar	50% Engel I
				50% Engel IV
Liu, et al. 2012[10]	18/18	14 lesional	lobar, lesionectomy, multilobar + MST and/ or Callosotomy	50% Engel I
				21.4% Engel II
				21.4% Engel II
				7.1% Engel IV
		4 nonlesional	lobar,lesionectomy,mul-tilobar, +MST and/or callosotomy	50% Engel II
				25% Engel III
				25% Engel IV
Lee, et al. 2014[17]	39/76	35 lesional	lobar, multilobar, hemipsherectomy	62.6% Engel I
				17.1% Engel II (6/35- 17.1%)
				11.4% Engel III (4/35- 11.4%)
				8.6% Engel IV (3/35- 8.6%)
		4 nonlesional	lobar	50% Engel I
				50% Engel II
Kang, et al. 2018[18]	90/90			
		70 lesional	hemispherectomy, lobar/multilobar	(53%) Engel I
		20 nonlesional	hemispherectomy lobar/multilobar	(40%)- Engel I

Keator, 2021

Callosotomy for atonic

- Highly variable outcomes
- Different definitions (atonic vs. drop attack)

	Seizure free	>75% reduction	>50% reduction
Rolston et al	58%		
Lancman et al	48%	70%	80%

Rolston, JD et al Epilepsy & Behavior 51 (2015)
Lancman, G et al, Seizure 22 (2013)

Treatment algorithm

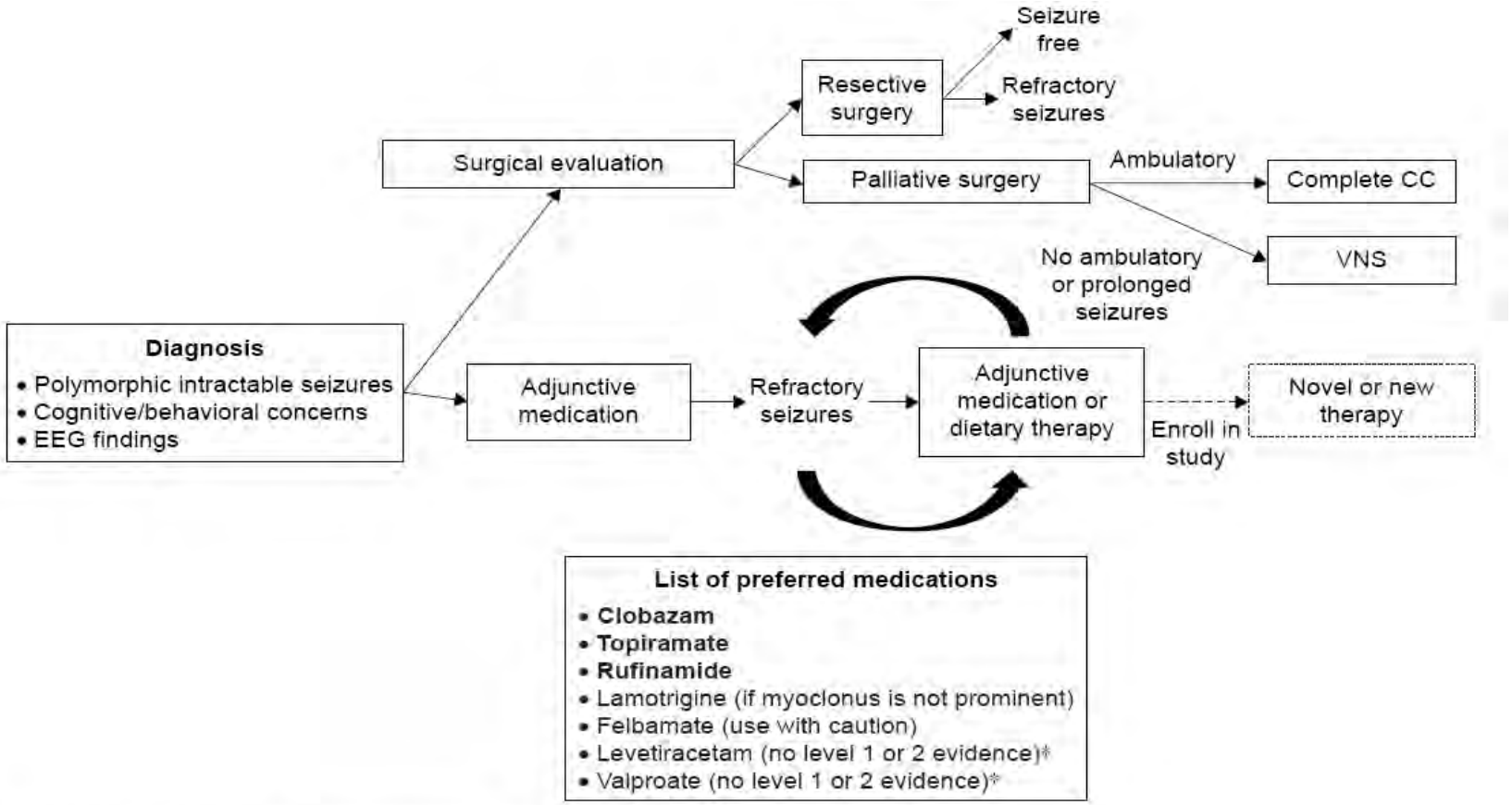
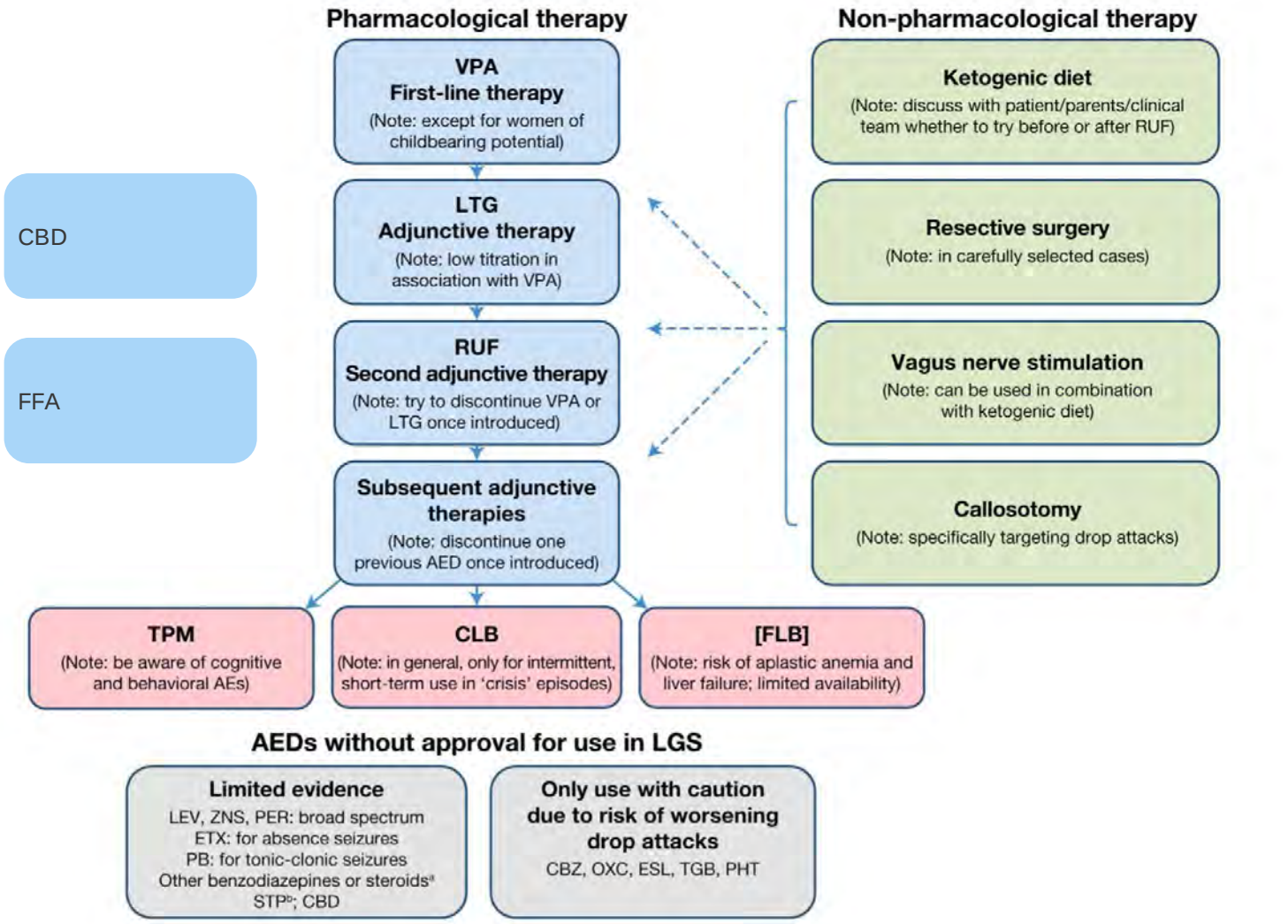


Figure 6 Proposed management of Lennox-Gastaut syndrome.
Notes: First-tier preferred medications are in bold. *Commonly used medications without level 1 or 2 evidence.
Abbreviations: CC, corpus callosotomy; EEG, electroencephalogram; VNS, vagal nerve stimulator.

Ostendorf AP and Ng YT, Neuropsychiatr Dis Treatment, 2017

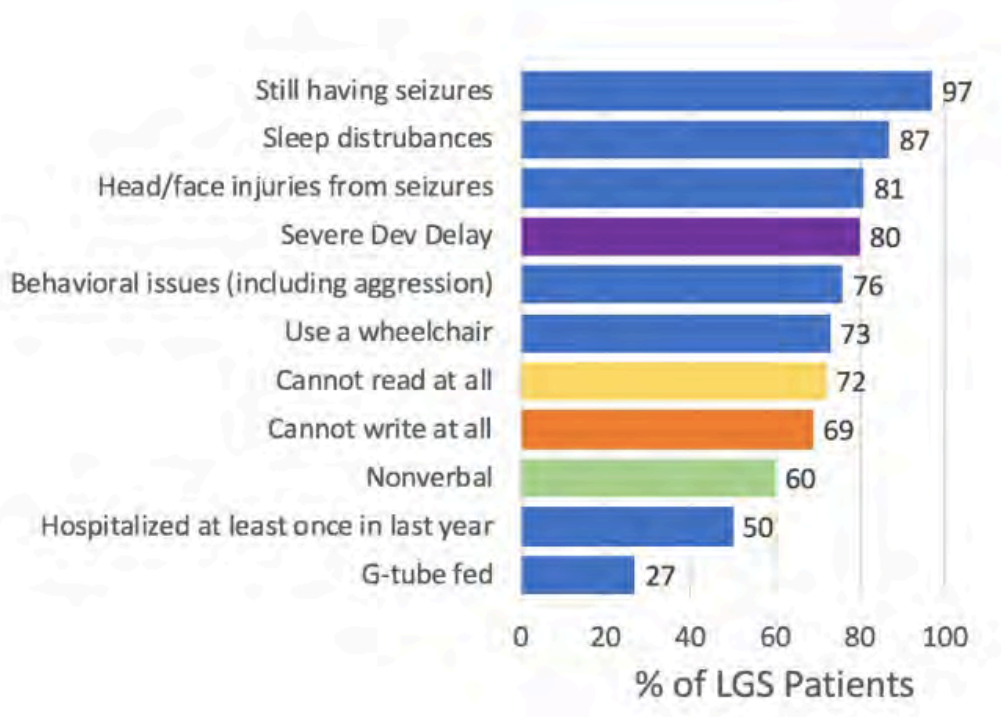
Expert opinion



Cross JH, et al. Frontiers in Neurology, Sept 2017

Rational polypharmacy

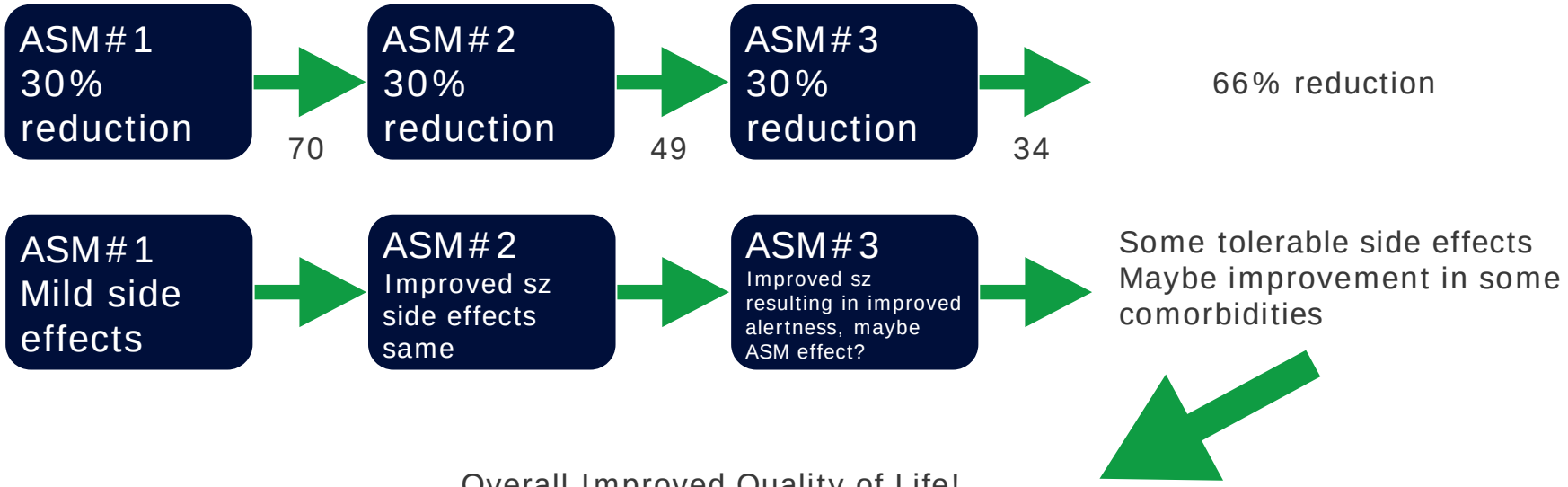
- Seizure freedom is highly unusual
- Leads to polypharmacy to achieve best seizure reduction possible
- Polypharmacy leads to increased likelihood of adverse events and possibly worsening of comorbidities
- Need to consider:
  - Drug interactions
  - Impact on comorbidities such as
    - sleep
    - cognition
    - behavior
    - motor function



Must remember to remove medications that are not working

Sequential add-on polytherapy

- GOAL-sequential reduction in seizures without adding or increasing clinically meaningful side effects
- Starting with 100 seizures/month



Key messages

- Establish goals of treatment with family, will require a balance of seizure control and QOL
- Many treatment options available including medications, devices, diet and surgery
- When using polytherapy, as is often required, ensure that there is a rationale in considering drug interactions and impact on QOL

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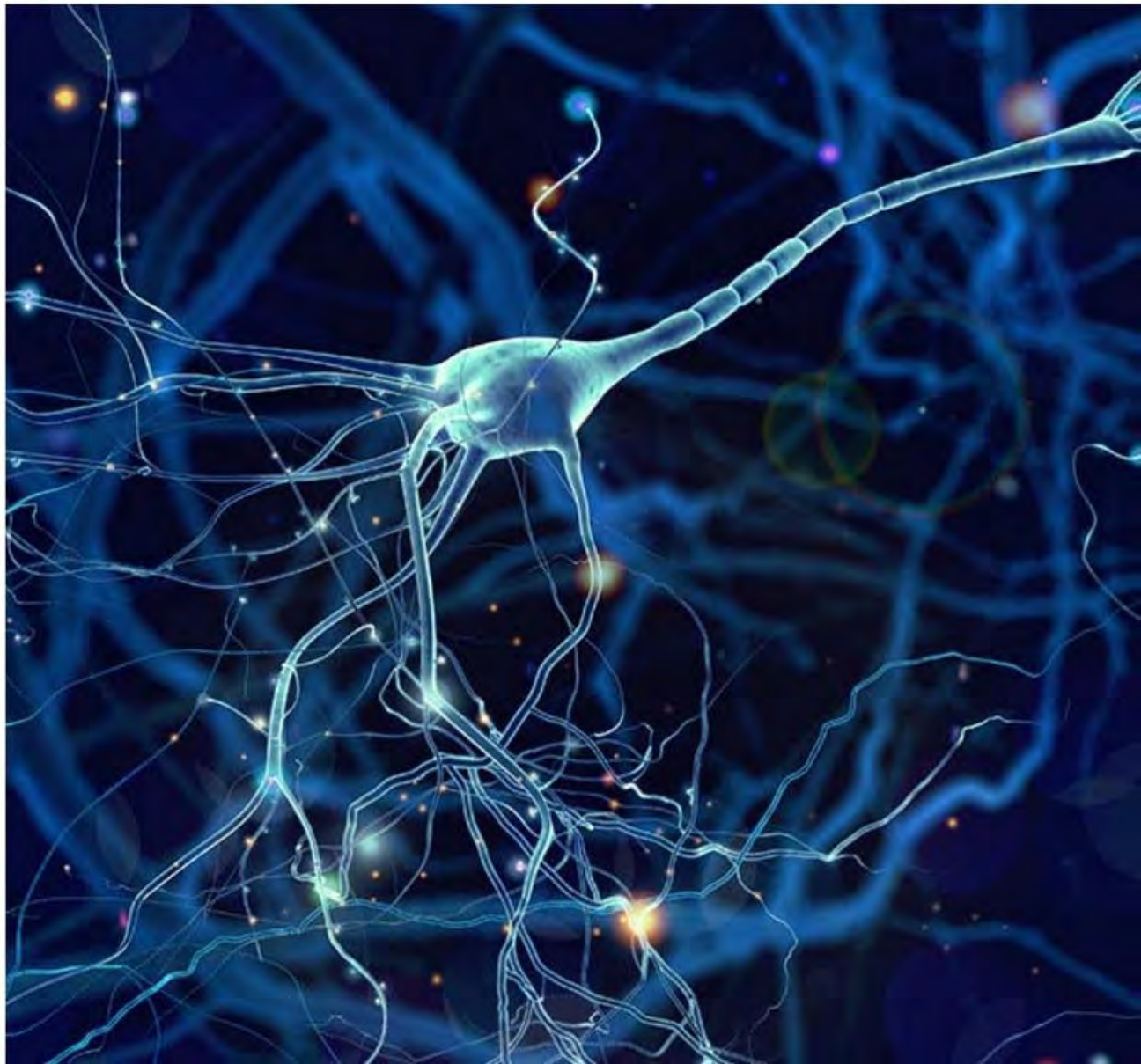
Understanding LGS: Management and Care Coordination



Rima Nabbout

MD, PhD

Professor of Pediatric Neurology, University Paris Cité, Paris, France

Objectives

- Definition of DE, EE and DEE
- LGS syndrome beyond seizures
- Multidisciplinarity and multimodal care
- Transition to adult care

Definitions

Developmental encephalopathy:

- Encephalopathy is DUE TO the underlying cause of the epilepsy, but NOT made worse by seizures or frequent epileptiform discharges

Epileptic encephalopathy:

- Encephalopathy is DUE TO frequent seizures and/or frequent epileptiform discharges
- Improvement in seizure control will improve encephalopathy

Developmental and epileptic encephalopathy:

- Where both components are present

Adapted from Wirrell et al., 2022

LGS criteria for diagnosis

	Mandatory	Alerts	Exclusionary
Seizures	Tonic seizures (see text) In addition to tonic seizures, at least one additional seizure type must be present, which may include any of the following: • Atypical absences • Atonic • Myoclonic • Focal impaired awareness • Generalized tonic–clonic • Nonconvulsive status epilepticus • Epileptic spasms		
EEG	Generalized slow spike-and-wave complexes of <2.5 Hz (or history of this finding on prior EEG) Generalized paroxysmal fast activity in sleep (or history of this finding on prior EEG)	Photoparoxysmal response at low frequencies (consider CLN2 disease)	Persistent focal abnormalities without generalized spike-and-wave pattern
Age at onset	<18 years	>8 years	
Long-term outcome	Drug-resistant epilepsy Mild to profound intellectual disability		

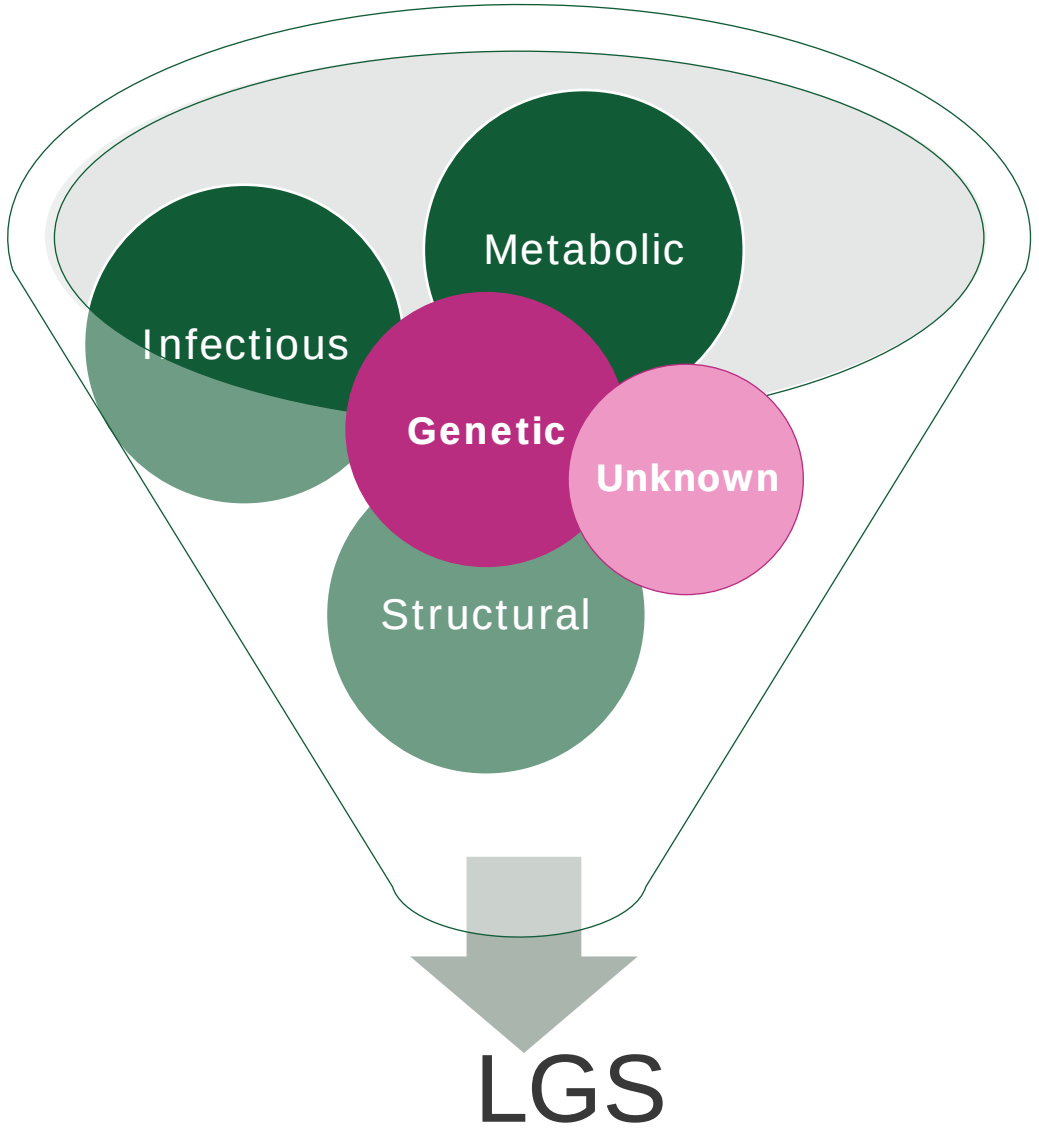
An MRI is not required for diagnosis but is usually performed to evaluate for underlying etiology.
An ictal EEG is not required for diagnosis. However, it should be strongly considered in a child with alerts or with clinical features that may suggest epilepsy with myoclonic atonic seizures syndrome.
Syndrome-in-evolution: Approximately 50% of infants with a severe DEE, e.g., IESS or early infantile DEE, evolve over time to Lennox–Gastaut syndrome.

Specchio et al., 2022

One syndrome with different etiologies

The etiology may impact:

- The age of onset
- The types of seizures
- The type of EEG abnormalities
- The level of EE/DEE/DE
- The severity of encephalopathy
- The outcome
- The response to therapies



Transition to adulthood

Keep in mind the disease beyond seizures!

- LGS persists into adulthood in nearly all cases

- **Seizures** remain **drug-resistant:**
  - Atypical absence and tonic seizures remain frequent in adults,
  - whereas atonic seizures often settle.

- Moderate to severe **intellectual disability present** in >90% of patients

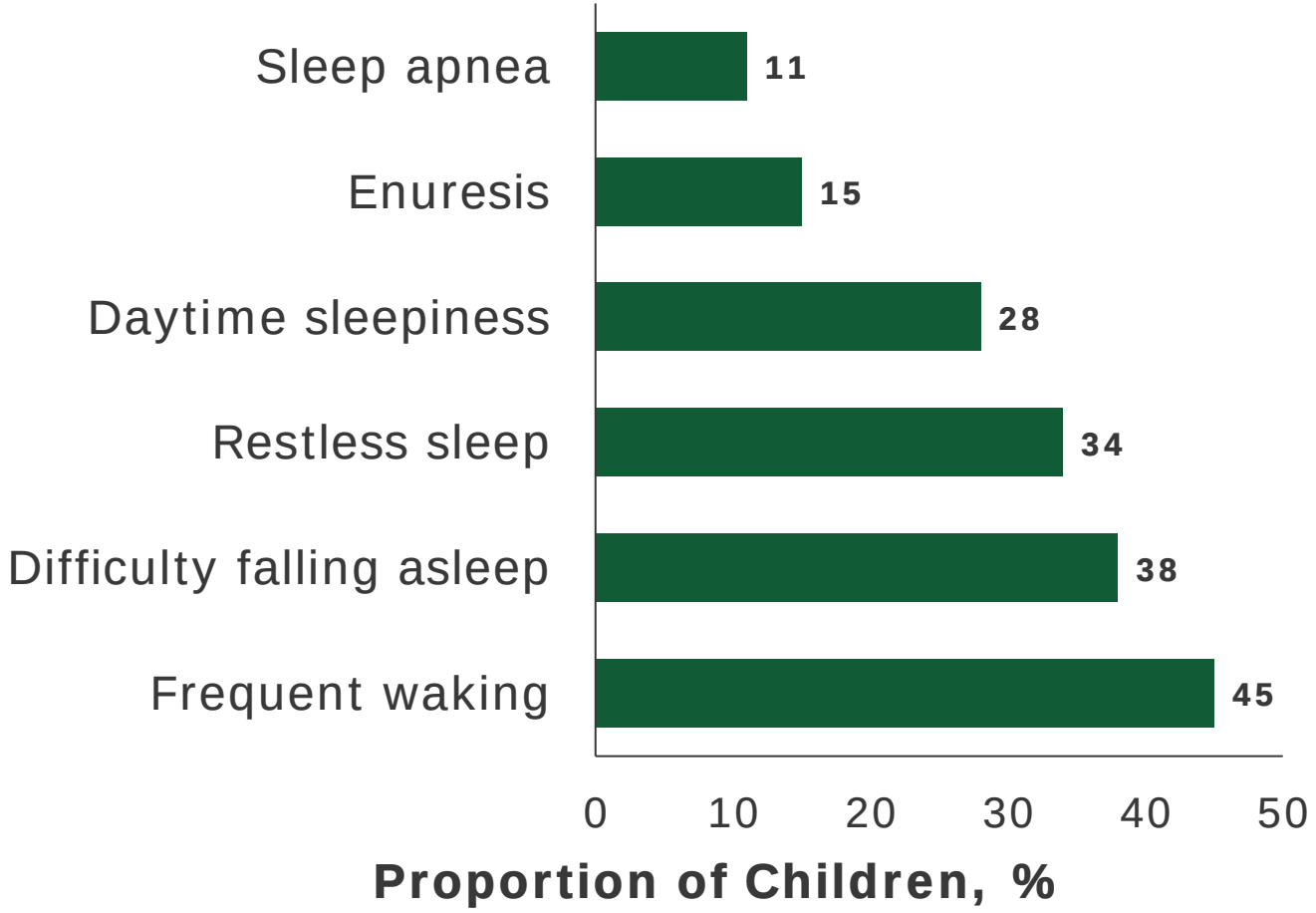
- **Behavior disorders** such as hyperactivity, aggression, autism spectrum disorder, and sleep disturbances are common in childhood and increase in adolescence and adulthood

Ferlazzo et al., 2010; Camfield et al., 2011; Kerr M, et al., 2011; Kim HJ, et al., 2015; Vignoli et al., 2017; Strzelczyk et al., 2023

Sleep problems

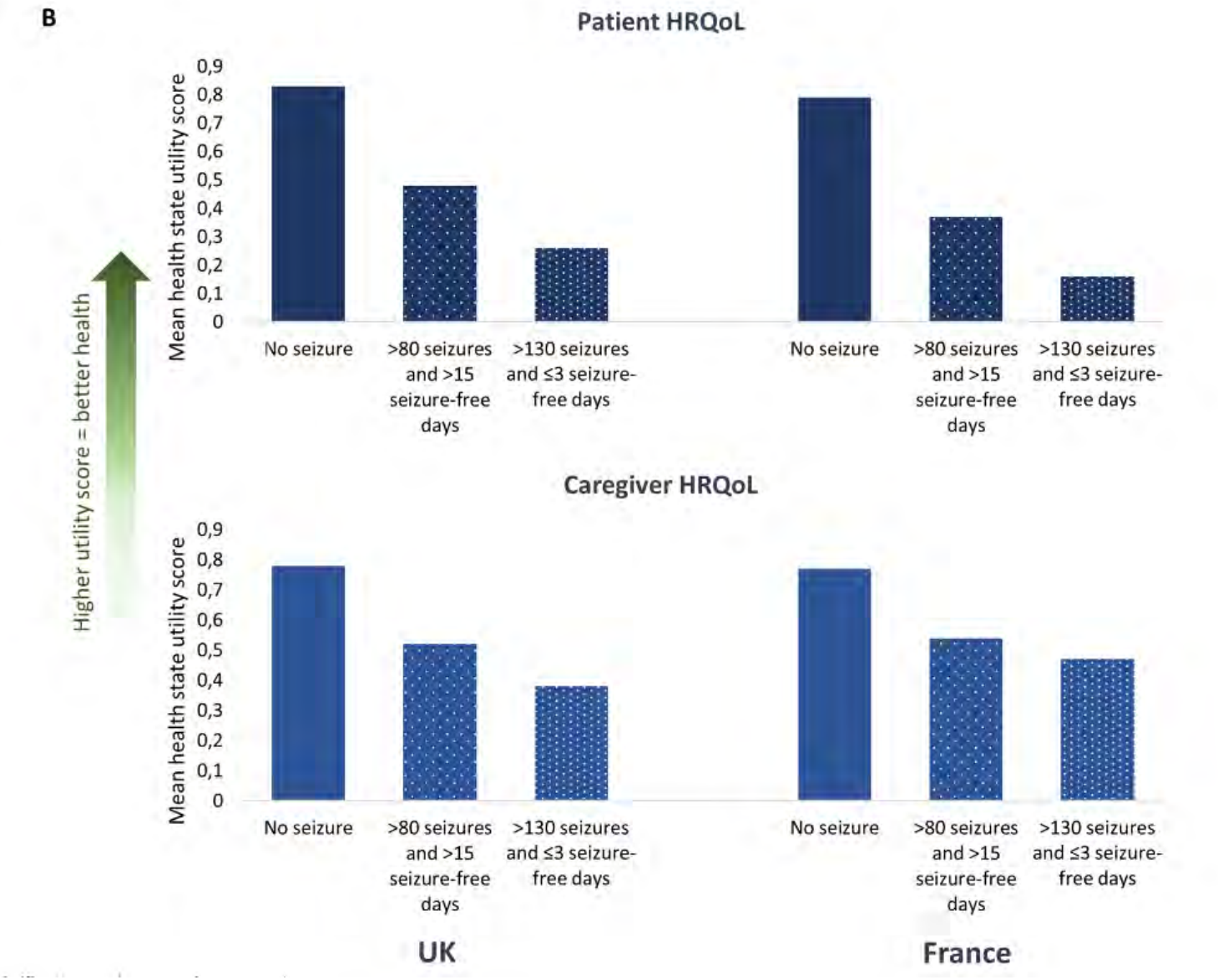
Sleep questionnaire completed by caregivers of children with rare epilepsies (N = 356)

- 53% reported sleep concerns:
  - More commonly reported in children with nocturnal seizures (*P* = .03)
  - Sleep problems more common with increasing age of child



Gupta G, et al. Pediatr Neurol. 2022;128:9-15.

HRQoL in relation to seizures and seizure-free days



Strzelczyk et al., 2023

BECOME (BEhavior, COgnition, and More with Epidiolex®)

To characterize and quantify nonseizure behavioral and cognitive outcomes in pediatric (<18 years) vs adult (≥18 years) patients from the cross-sectional caregiver survey BECOME

- US-based caregivers **(N=498) of patients with LGS (80%) or DS (20%) who received ≥3 months of CBD treatment** (Epidiolex®, 100 mg/mL oral solution) compared the past month with the period before CBD initiation
- Mean age of patients: 16 (11) years, median concomitant ASMs: 4
- For adult patients, the most common improvement was in alertness (70%).
- A substantial proportion of caregivers of patients with LGS or DS, regardless of age, reported improvements in outcomes beyond seizure control since initiating CBD treatment.

Dixon Salazar et al., 2023

Claire, 12 y girl with Lennox-Gastaut syndrome

- Diagnosed with infantile epileptic spasms syndrome at age 7 months and treated with high dose oral steroid and vigabatrin. Spasms relapsed at 10 months and have been drug resistant

- Over time, has developed nightly tonic seizures, daily atonic drops and atypical absences and weekly generalized tonic-clonic seizures
- EEG shows paroxysmal fast activity in sleep and generalized 2 Hz slow spike-wave
- Extensive testing (MRI, genetic and metabolic studies) are unrevealing

- She is in a specialized education program with a rehabilitation program tailored for her needs
- She is with her family during nights, weekends and holidays
- The coordination of care is handled by her pediatric neurologist, her center and her family

Claire, now 17 years old

- Some improvement in seizures on new available ASM
- Still having 1-2 subtle tonic seizures each night, each lasting <5 seconds, GTCS are twice monthly
- She has severe ID and autism spectrum disorder
- Her family is finding it difficult to manage her aggressive behavior
- She also has disrupted sleep making nights difficult for the whole family

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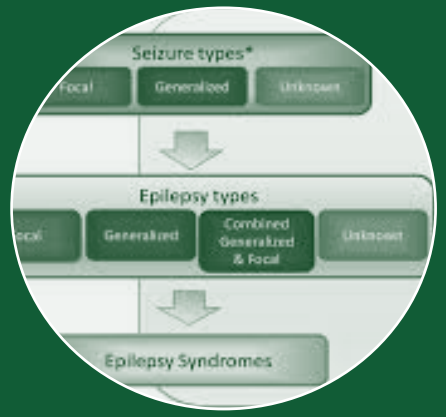
Preparing the transition to adult care:

- Adult epileptologist asked many questions on her new ASMs and on her ID
- Psychiatrist is not sure of his role for adults with ASD and ID with epilepsy
- Adult home care can handle the seizures and lack of autonomy but not the behavior
- The family is unable to be as present as before with the mother on chemotherapy!

Transition: no size fits all!



Epilepsy and syndromes outcomes

Complexity of the needs and interventions

The local context of care

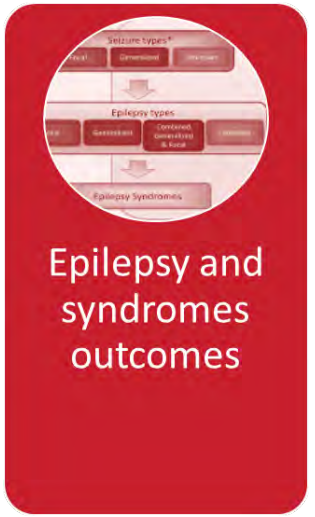
Gender?

Core set transition program with a personalized path for each patient

DEEs transition to adult care in LGS

Changes in seizures and seizures' therapies

- Change in type, duration, sleep/awake occurrence, trigger factors, impact …and in some instances frequency
- **Some LGS therapies** are less used in adults (fenfluramine, cannabidiol and ketogenic diet)
- The impact of ASMs can be different on comorbidities in adolescents and adults
- Consider the drug-to-drug interactions in women with medical contraception and efficacy of contraception



The transition beyond seizures?

Changes in comorbidities and their impact:

Intellectual disability and autonomy

Psychiatric and behavior disorders

Motor and movement disorders

Sleep disorders

Eating and GI disorders

Changes in the coordination of care:

- Who is the care coordinator after the pediatric neurologist and the family?
- How to handle the different needs and multidisciplinarity?

- Sexual function, contraception, reproductive toxicities
- Changes in legal status: capacity, consent, best interest

Multidisciplinarity in medical care and beyond

Minimum pediatric experts involved:

- Child neurologist/epileptologist
- Child psychiatrist
- Gastroenterologist
- Orthopedic surgeon
- Epilepsy nurse (in some countries)

With a team of rehabilitation:

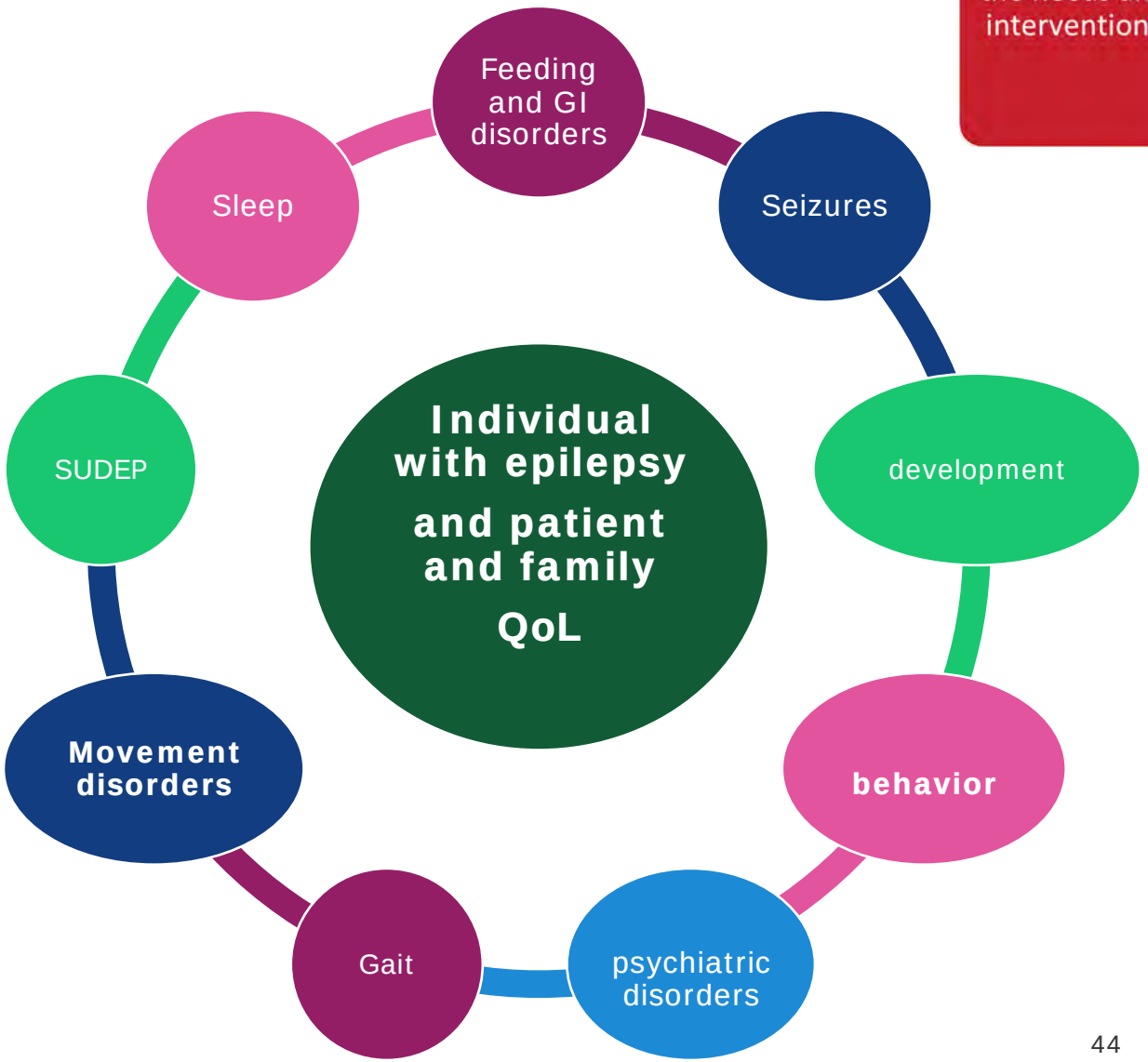
Psychomotricity

Speech therapy

Physiotherapist and occupational therapist

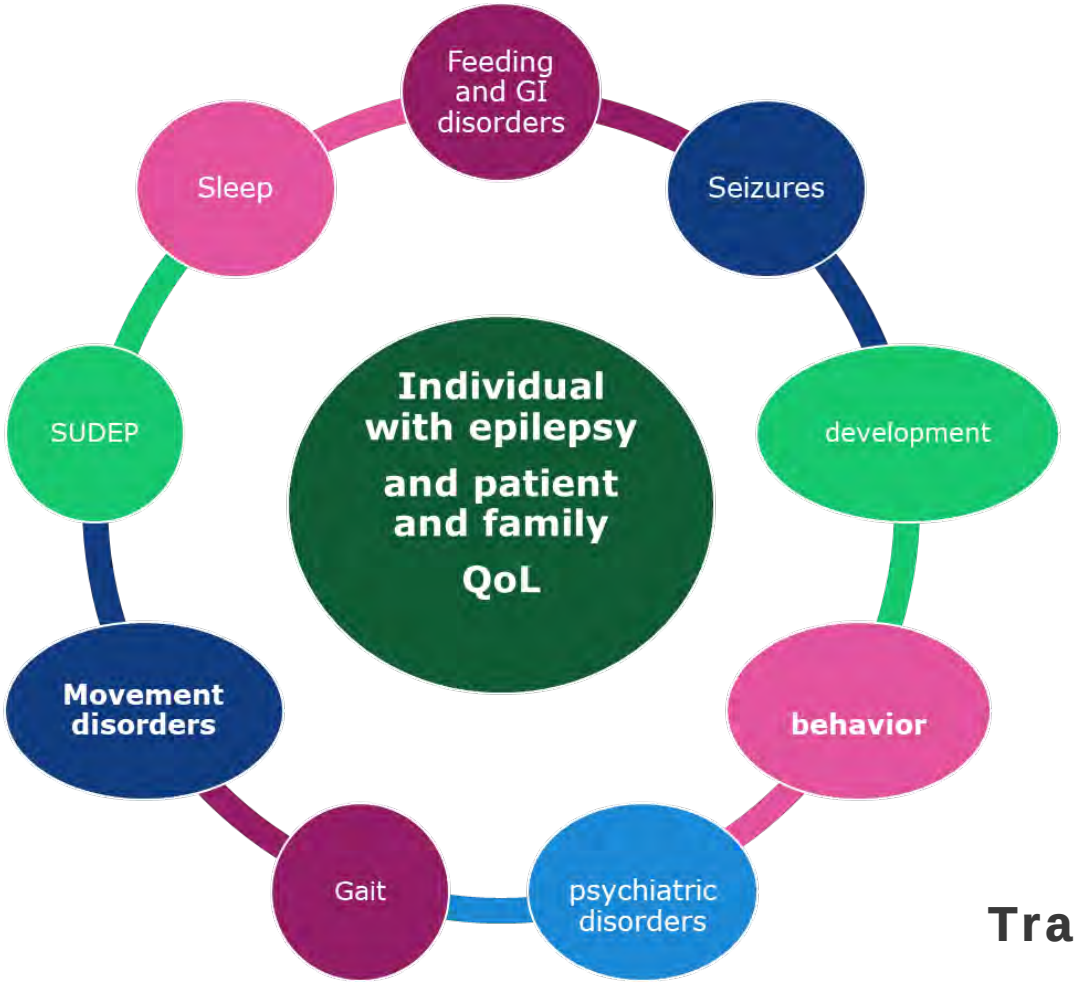
Special education team

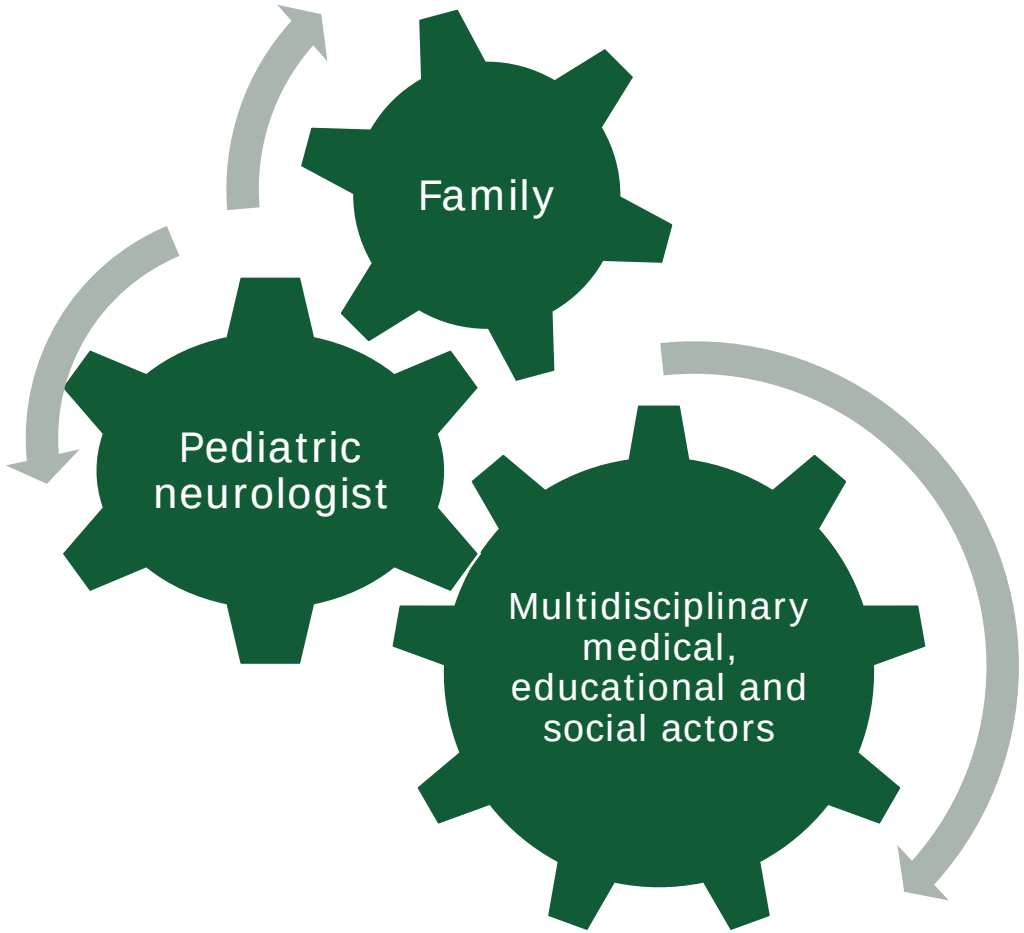
Psychologist



Coordination of the multidisciplinary care

A critical issue during transition and transfer





Translate this pediatric organisation to adult care through transition programs

Key messages

- Lennox-Gastaut syndrome is a DEE syndrome-in-evolution as other DEEs may evolve to LGS
- Intellectual disability is often moderate to severe
- Psychiatric and behavioral comorbidities are major issues all life long
- LGS is a lifelong disease that requires specific preparation for the transition and transfer to adult care, ensuring multimodal care
- Transition should be personalized as no size fits all!