Can we reach our goals for seizure management in drug-resistant focal epilepsy?

Disclaimer

- *Unapproved products or unapproved uses of approved products may be discussed by the faculty; these situations may reflect the approval status in one or more jurisdictions*
- *The presenting faculty have been advised by touchIME to ensure that they disclose any such references made to unlabelled or unapproved use*
- *No endorsement by touchIME of any unapproved products or unapproved uses is either made or implied by mention of these products or uses in touchIME activities*
- *touchIME accepts no responsibility for errors or omissions*

touch NEUROLOGY®

Drug-resistant epilepsy: What does it mean for patients?

Dr Christian Brandt

Bethel Epilepsy Centre
Mara Hospital, Bielefeld, Germany

touch NEUROLOGY®

Prevalence of drug-resistant epilepsy

- DRE is a significant clinical challenge
- The prevalence of DRE is approximately 30% in epilepsy patients
- The incidence of DRE does not vary geographically

DRE, drug-resistant epilepsy.

Kalilani L, et al. *Epilepsia*. 2018;59:2179–93.

ILAE definition of drug-resistant epilepsy

DRE refers to the failure of adequate trials of **two** appropriate AED regimens to achieve sustained seizure freedom[1]

Appropriate dose and frequency of a well-tolerated AED for a sufficient length of time (mono- or combination therapy)

AED previously shown to be effective in the patient's epilepsy seizure and type, preferably in RCT

No seizures or auras for ≥3 times the longest interseizure interval in the 12 months prior to the AED trial

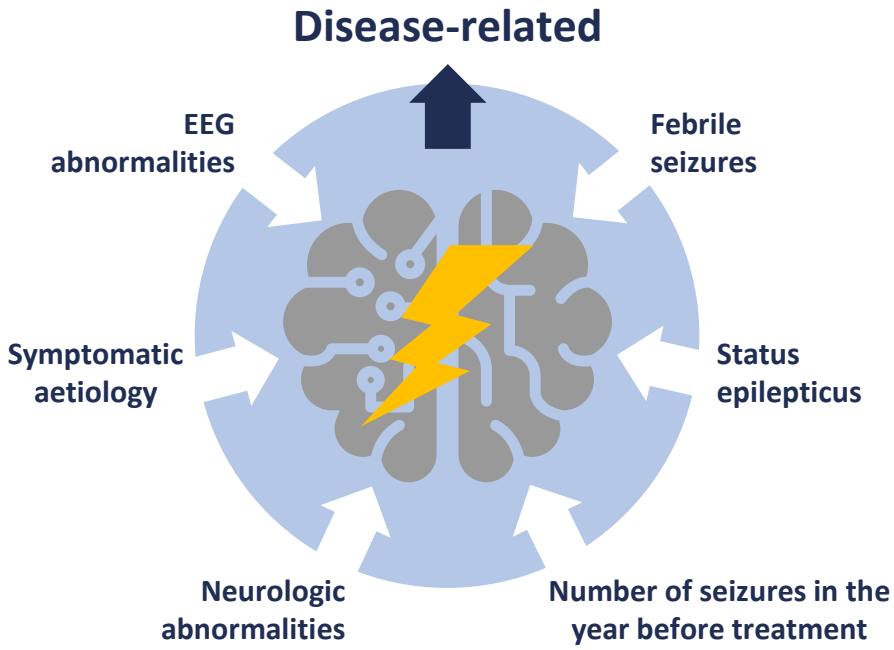
Common deviations from the ILAE definition in DRE reporting:[2]

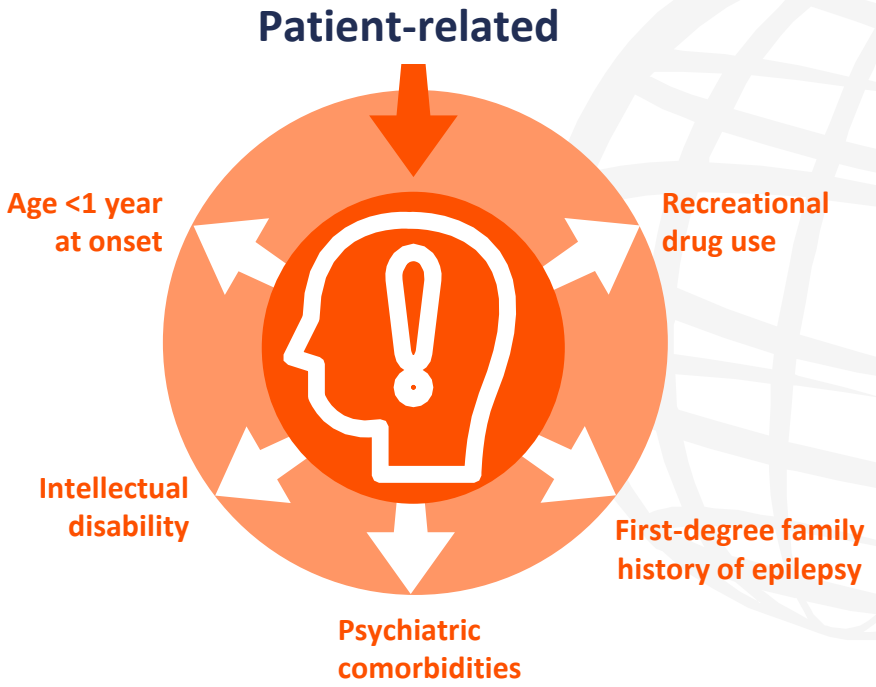
- Greater or fewer numbers of failed AEDs
- Shorter or longer follow-up period
- Not all components of AED treatment (trial) adequacy included

AED, anti-epileptic drug; DRE, drug-resistant epilepsy; ILAE, International League Against Epilepsy; RCT, randomized controlled trial.

1. Kwan P, et al. *Epilepsia*. 2010;51:1069–77; 2. Kalilani L, et al. *Epilepsia*. 2018;59:2179–93.

Potential risk factors for drug-resistant epilepsy[1,2]





EEG, electroencephalography.

1. Kalilani L, et al. *Epilepsia*. 2018;59:2179–93; 2. Löscher W, et al. *Pharmacol Rev*. 2020;72:606–38.

touch NEUROLOGY®

Quality of life in people with epilepsy

Requirement for screening tools to detect factors that negatively impact QoL

QoL impairment

- Depression
- Lack of perceived self-mastery
- Anxiety
- Felt stigma
- High seizure frequency

- Depression and anxiety are often under-diagnosed in epilepsy with persistent seizures
- Educational, psychological and social interventions may be needed alongside pharmacological therapy

QoL, quality of life.

Ridsdale L, et al. *J Neurol*. 2017;264:1174–84.

Current approaches to drug-resistant epilepsy: Have we reached our goal?

Dr Manuel Toledo

Vall d'Hebron University Hospital
Barcelona, Spain

Potential causes of pseudo-resistance to AEDs

Diagnostic uncertainty and failure to classify patients can contribute to pseudo-refractoriness[1]

Diagnosis-related[1–3]

- **Incorrect seizure type**
- **Non-epilepsy syndromes/diagnoses**
  syncope, cardiac arrythmia, migraine, TIA
- **Psychogenic non-epileptic seizures**
- **Potential candidate for surgical treatment**

→ **Thorough re-evaluation is required**

AED-related[1,2]

- **Incorrect drug for seizure type**
- **Insufficient dose/frequency**
- **Poor adherence**

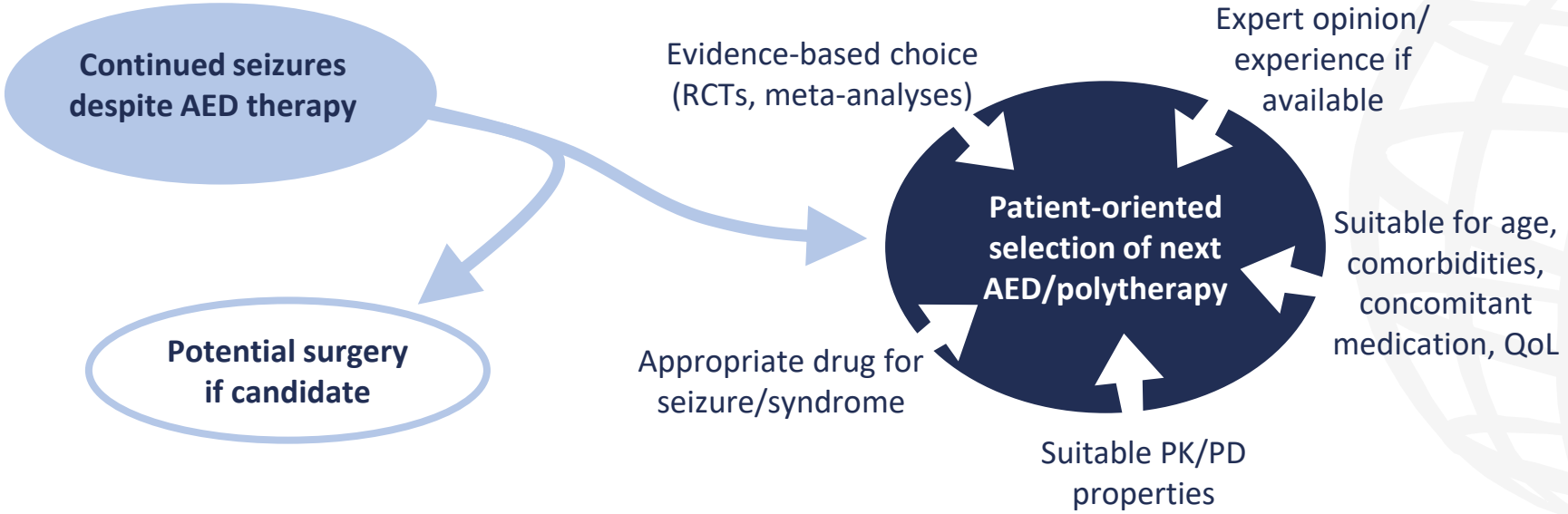
→ **Rational drug trials recommended**

AED, anti-epileptic drug; TIA, transient ischaemic attack.

1. Park KM, et al. *J Epilepsy Res*. 2019;9:14–26; 2. Dalic L, Cook MJ. *Neuropsychiatric Dis Treat*. 2016;12:2605–16; 3. Anzellotti F, et al. *Front Neurol*. 2020;11:461.

Therapy selection in drug-resistant focal epilepsy

Current standard of care relies on a trial and error approach for sequential AED regimens



AED, anti-epileptic drug; PK/PD, pharmacokinetics/pharmacodynamics; QoL, quality of life; RCT, randomised controlled trial.
Park KM, et al. *J Epilepsy Res*. 2019;9:14–26.

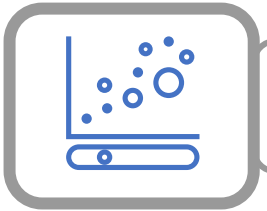
touch NEUROLOGY®

Polytherapy and management challenges

Concurrent use of AEDs increases the risk of adverse effects and drug–drug interactions

Factors affecting choice of adjunctive therapies

Preferred AEDs at centre
Previous efficacy in patient
Patient's comorbidities



PK interactions with AEDs
Drug–drug interactions with non-AEDs
High therapeutic index

Advantageous/synergistic MOA
Different adverse events to current therapy

Comorbidities to consider

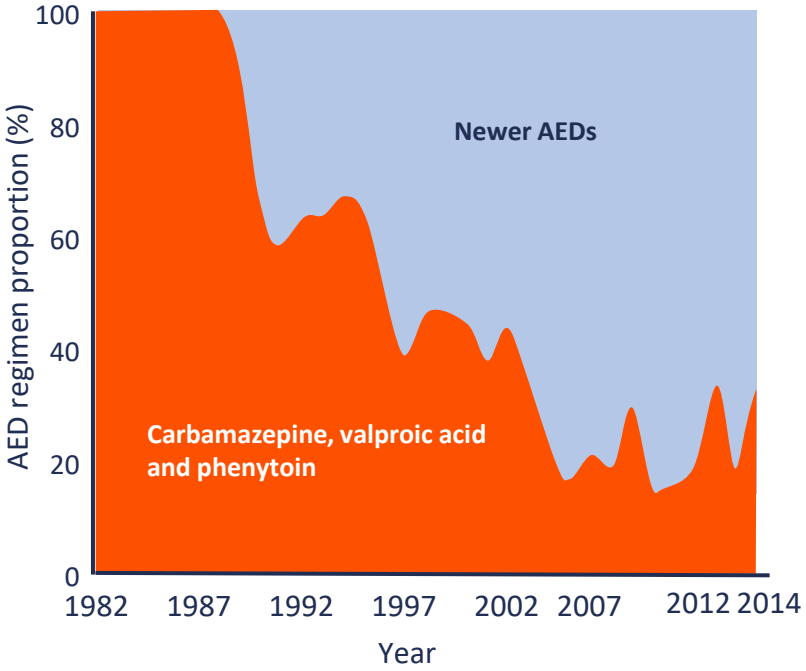
- Psychiatric conditions
- Anxiety/depression
- Cognitive dysfunction
- Tremor/parkinsonism
- Migraine
- Obesity
- Skin rash
- Neuropathy
- Hepatic/renal function
- Cardiac arrythmia
- Atherosclerosis
- Cancer

AED, anti-epileptic drug; MOA, mechanism of action; PK, pharmacokinetic.
Park KM, et al. *J Epilepsy Res*. 2019;9:14–26.

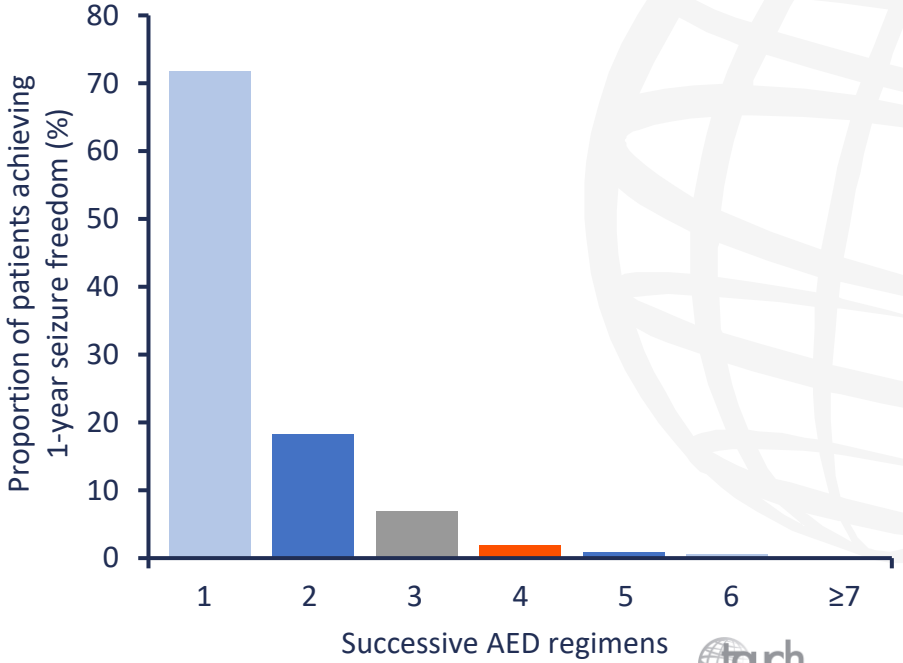
Effect of new AED availability on seizure freedom

30-year longitudinal cohort study

AED prescriptions and availability



Seizure freedom with successive regimens
1,144/1,795 patients achieved seizure freedom (64%)



AED, anti-epileptic drug.

Chen Z, et al. *JAMA Neurology.* 2018;75:279–86.

touch NEUROLOGY®

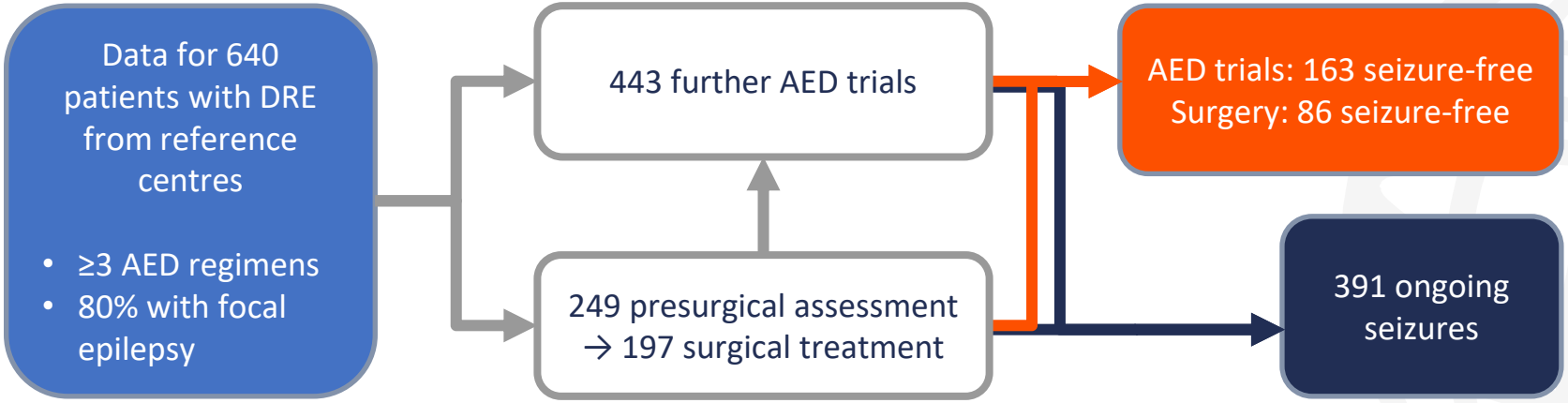
Optimizing treatment of patients who are drug-resistant: Is seizure freedom a realistic goal?

Prof. Louise Tyvaert

University Hospital of Nancy
Nancy, France

Treatment trajectories in patients with drug-resistant epilepsy

Scope for ongoing development of novel treatments for DRE



- 163 of 443 (37%) of patients who underwent further AED trials achieved seizure freedom for ≥1 year

AED, anti-epileptic drug; DRE, drug-resistant epilepsy.
Conte F, et al. *Eur J Epilepsy*. 2018;62:74–8.

Considerations for referral to an epilepsy specialist centre

One or more criteria are present

- Child aged <2 years
- Epilepsy not controlled on medication within 2 years
- Management not successful after two drug regimens
- Patient at risk of unacceptable medication side effects
- Unilateral structural lesion
- Psychological or psychiatric comorbidity
- Diagnostic doubt as to nature of seizures/syndrome

NICE Clinical guideline. Epilepsies: diagnosis and management. Updated February 2020. Available at: www.nice.org.uk/guidance/cg137 (accessed October 2020).

Effect of reduced seizure frequency on QoL and mortality

Pre- and post-operative registry data from 550 patients[1]

73% Mean relative seizure reduction

67% Seizure-free at last follow-up

49.8 →42.1 Decrease in mean LSSS seizure severity score

27.8 →22.5 Significant improvement in mean QOLIE-10 score

8.5 →6.4 Significant decrease in mean PHQ-9 depression score

9.5% →37.3% Significant increase in patients able to drive

American Epilepsy Society Guidelines[2]

Risk of sudden unexpected death in epilepsy based on 12 Class I studies

Children ≤17 years old	Adults
0.22	**1.20**
per 1000 patient-years 95% CI 0.16–0.31	per 1000 patient-years 95% CI 0.64–2.32

- Seizure freedom strongly associated with decreased risk of sudden unexpected death
- Not being seizure-free for 1–5 years increased the risk of sudden unexpected death **4.7-fold**

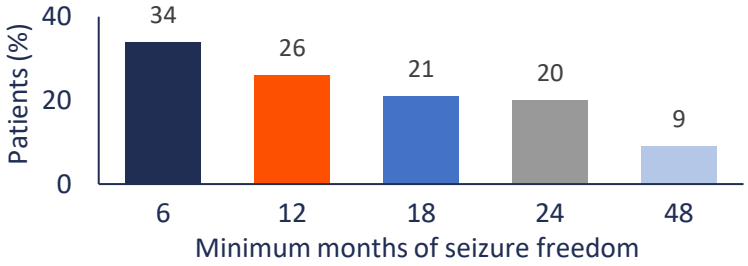
CI, confidence interval; LSSS; Liverpool Seizure Severity Scale; PHQ-9; Patient Health Questionnaire-9; QoL, quality of life; QOLIE-10, Quality of Life in Epilepsy-10 inventory.

1. Sheikh S, et al. *Epilepsia.* 2019;60:2078–85; 2. Harden C, et al. *Epilepsy Curr.* 2017;19:180–7.

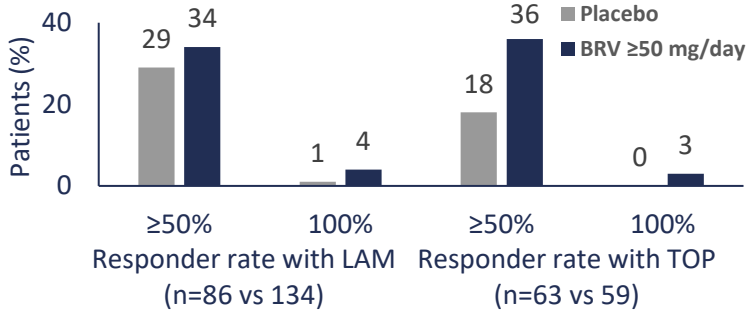
Potential for seizure freedom with novel agents

Brivaracetam[1,2]

Monotherapy (86 adults with ≥6 months' exposure)

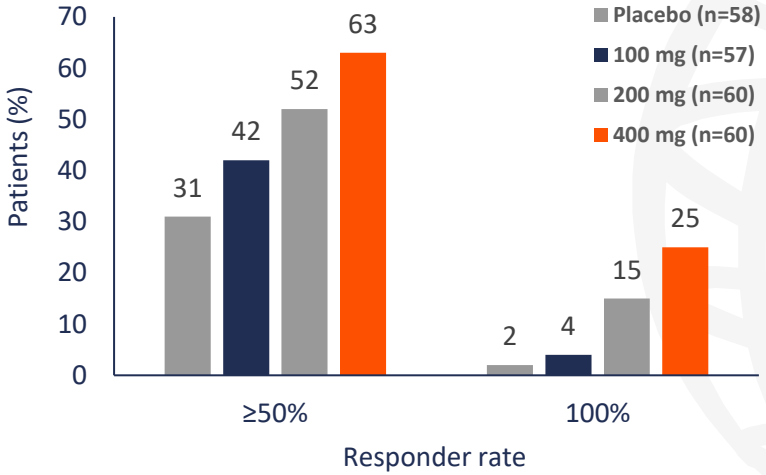


Adjunctive therapy with LAM or TOP



Cenobamate[3]

Adjunctive therapy with 1–3 AEDs (European patient subgroup)



- Seizure freedom occurred in 4/15/25% of patients who received 100/200/400 mg cenobamate vs 2% for placebo
- Data consistent with outcomes in overall population

AED, anti-epileptic drug; BRV, brivaracetam; LAM, lamotrigine; TOP, topiramate

1. Arnold S, et al. *Epilepsy Res*. 2020;166:106404; 2. Benbadis S, et al. *Epilepsy Behav*. 2018;80:129–34; 3. Brandt C, et al. *Eur J Neurol.* 2020;27(Suppl. 1):148.

touch NEUROLOGY®