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REVIEW

# Clinical Management of Drug Resistant Epilepsy: A Review on Current Strategies



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**Abstract:** Drug resistant epilepsy (DRE) is defined as the persistence of seizures despite at least two syndrome-adapted antiseizure drugs (ASD) used at efficacious daily dose. Despite the increasing number of available ASD, about a third of patients with epilepsy still suffer from drug resistance. Several factors are associated with the risk of evolution to DRE in patients with newly diagnosed epilepsy, including epilepsy onset in the infancy, intellectual disability, symptomatic epilepsy and abnormal neurological exam. Pharmacological management often consists in ASD polytherapy. However, because quality of life is driven by several factors in patients with DRE, including the tolerability of the treatment, ASD management should try to optimize efficacy while anticipating the risks of drug-related adverse events. All patients with DRE should be evaluated at least once in a tertiary epilepsy center, especially to discuss eligibility for non-pharmacological therapies. This is of paramount importance in patients with drug resistant focal epilepsy in whom epilepsy surgery can result in long-term seizure freedom. Vagus nerve stimulation, deep brain stimulation or cortical stimulation can also improve seizure control. Lastly, considering the effect of DRE on psychologic status and social integration, comprehensive care adaptations are always needed in order to improve patients' quality of life.

**Keywords:** drug resistant epilepsy, epilepsy surgery, antiseizure drugs, comprehensive care

## Definition of Drug Resistant Epilepsy

Drug resistant epilepsy (DRE) is defined by the International League Against Epilepsy (ILAE) as the persistence of seizures despite at least two syndrome-adapted antiseizure drugs (ASD) used at efficacious daily dose.[1] According to this definition, the single variable that should be considered is whether or not the patient is seizure-free. In contrast, neither the type of seizures, the seizure frequency nor the other epilepsy-related complications are included in this definition. However, the latter drive the handicap resulting from DRE and its consequence on quality of life (QOL) at the individual patient level and will be considered in the therapeutic management of DRE.

Several issues need to be underscored:

- The minimum duration required to evaluate the response to an ASD might vary across patients, especially depending on the baseline seizure frequency. For a patient with several seizures per week, a follow-up of several weeks will be enough to conclude on ASD failure if seizures persist. In contrast, the evaluation period will be much longer for a patient with 1–2 seizures per year.

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- The threshold of two ASD may look arbitrary: it is related to the patterns of treatment response reported in prospective cohorts of epilepsy.[2–4] The probability of seizure-freedom after two ASD failures decreases exponentially and is less than 5% after four failures.[4,5] It should however be reminded that spontaneous or treatment-related seizure-free period of a minimum 12 months duration is reported in almost 20–25% of adult with DRE, with an annual rate of approximately 5%.[6,7] When the analysis is limited to patients not eligible for epilepsy surgery, the cumulative probability of achieving a 12-month seizure remission period is of 33% at 7 years.[8] Although this remission is typically transient, with 71% of patients relapsing within 5 years,[8] these data might comfort the possible benefit at individual patient level of continuing to modify the ASD regimen, even after several failures. This might particularly be relevant for patients with frequent generalized-tonic seizures, especially considering the potential impact of this active management on the risk of sudden unexpected death in epilepsy (SUDEP).[9]
- Only half of patients with uncontrolled seizures might meet the ILAE criteria of DRE,[10] suggesting the importance of re-evaluating patient's epilepsy history before conclusion. In a study evaluating the interrater agreement of the ILAE DRE definition between members of an epilepsy expert panel and individual investigators, 19% of patients were classified as having DRE by the investigators while considered to have "undefined responsiveness" by the expert panel.[11] These divergences were mostly related to ASD dosage and/or the choice of the previously failed ASD.
- ASD prematurely withdrawn before having been titrated up to efficacious dose because of adverse events are not be considered as a failure for DRE criteria.
- Distinguishing drug-resistance from "pseudo-resistance":
  - Treatment compliance needs to be systematically evaluated.[12] Beliefs about medications, mood or anxiety disorders, recent uncontrolled seizures, multiple dosage schedule, poor physician–patient relationship are factors of poor adherence.[12]
  - Psychogenic non-epileptic seizures possibly lead to 20 to 25% of pseudo-resistance.[13] This issue reinforces the importance of detailed diagnostic work-up in patients who develop drug-resistance, including long-term video-EEG when the description of the ictal semiology is not clear enough to exclude the occurrence of psychogenic non-epileptic seizures. This is particularly relevant in patients who suffer from both epileptic and psychogenic non-epileptic seizures.
  - Using inefficacious, or even worsening, ASD for a dedicated epilepsy syndrome can also result in "pseudo-resistance". This issue has mostly been observed in patients with idiopathic generalized epilepsy, including childhood/adolescent absence epilepsy or juvenile myoclonic epilepsy, in whom some ASD, such as carbamazepine, phenytoin or gabapentin, can aggravate seizure frequency or precipitate status epilepticus.[14] Importantly, distinguishing idiopathic generalized epilepsy from focal epilepsy may not be trivial in daily clinical practice. Focal symptoms can be reported at the onset primary generalized epilepsy seizures.[15] Furthermore, focal EEG abnormalities can be observed in primary generalized epilepsies[16] whereas generalized EEG features have been reported in 20–67% of frontal lobe seizures.[17]

## Epidemiology and Risk Factors

The prevalence of DRE is 30% (95% CI: 19–42%). Its incidence varies from 15% (95% CI: 11–19%) in children to 34% (95% CI: 6–62%) in adults[18] without variation across geographic areas. Among patients with newly diagnosed epilepsy followed for at least two years in the Glasgow cohort, 36% were not seizure free the last year of follow-up.[5] The response to treatment was dynamic, with 37% of patients achieving immediate seizure freedom at the beginning, 22% suffering from initial relapses before persistent seizure-freedom, 16% with long-term DRE despite periods of transient remission.[2] Overall, 25% of patients were always drug resistant.[2] Despite the increasing number of available ASD, this picture has remained unchanged. The long-term follow-up of the Glasgow cohort thus showed that the proportion of newly diagnosed patients who developed DRE has not been modified over the past twenty years, at 64% in 2000 and 63.7% in 2018, despite the continual increase in the use of the new ASDs.[5]

**Table 1** Risk Factors for Developing Drug Resistant Epilepsy

| Risk Factors | Odd Ratio (95% Confidence Interval) |
|---|---|
| Age at onset | 5.49 (2.99-10.06) |
| Symptomatic epilepsy | 3.42 (2.21-5.27) |
| Abnormal EEG | 2.08 (1.16-3.74) |
| Febrile seizure | 1.31 (1.02-1.68) |
| Abnormal neurologic image | 2.78 (1.91-4.05) |
| Intellectual disability | 3.38 (2.16-5.31) |
| Neurologic abnormality | 8.61 (2.96-24.99) |
| Status epilepticus | 3.30 (2.36-4.63) |
| Psychiatric comorbidities | 1.93 (1.60-2.33) |

**Note:** Adapted from Kalilani L, Sun X, Pelgrims B, Noack-Rink M, Villanueva V. The epidemiology of drug-resistant epilepsy: a systematic review and meta-analysis. Epilepsia. 2018;59(12):2179/–2193. doi:10.1111/epi.14596.[18]

As shown in Table 1, several factors are associated with the risk of evolution to DRE in patients with newly diagnosed epilepsy. Although a lot of variations in the definitions of the risk factors across studies limit the interpretation of available epidemiological data, the factors with the strongest association with DRE are epilepsy onset in the infancy, intellectual disability, symptomatic epilepsy and abnormal neurological exam.[18] Although number of seizures before treatment initiation has been suggested to be a risk factor for DRE, delaying treatment initiation in patients who have presented one or two seizures does not modify the probability of achieving seizure freedom.[19] Better identification of patients at high risk of DRE at treatment initiation remains an important challenge. A machine learning approach identified patients at high risk of DRE two years earlier than the current practice.[20] However, patterns of evolution vary among patients, with in some patients DRE present at onset;[3] but other experience a relapse-remitting pattern.[2]

DRE can occur in all types of epilepsy syndromes, though the risk differs across them. In particular, although idiopathic generalized epilepsies are often considered as drug responsive, the long-term remission rates ranges from 64% to 82% of treated patients.[21,22] Long-term follow-up data thus shows that the proportion of patients who suffer from seizures despite ASD, even at low annual rate, is almost similar as the proportion of drug-resistance in adult focal epilepsy.[23,24] Poor outcome factors for idiopathic generalized epilepsies were recently evaluated[25] and were early seizure onset (before 13 years), multiple types of generalized seizures, history of status epilepticus, EEG with epileptiform activity (mainly polyspikes) and side effects of ASD. Resistance to sodium valproate was found to be the most important prognostic factor for refractory seizures[26] and suggest that "drug resistant idiopathic generalized epilepsies" may not be considered unless patients have been treated with sodium valproate.

In patients with epilepsy related to a genetic etiology, drug-resistance is particularly frequent, especially in those with severe developmental and epileptic encephalopathies. For instance, drug-resistance is virtually observed in all patients with Dravet Syndrome.[27,28] However, SCN1A mutations, which are associated with Dravet syndrome, can also be associated with Genetic Epilepsy with Febrile Seizures Plus (GEFS+),[29] resulting in potential implications for treatment specially to avoid pseudo-resistance. In addition, some Single Nucleotide Polymorphisms (SNPs) of the intronic regions of the SCN1A genes are significantly associated with drug resistance,[30] thus emerging as potential risk factors for drug resistance.

Concerning adult focal epilepsies, a great variability exists across the underlying etiologies. A diagnosis in the second decade of life, with more than one seizure with impaired awareness per month, mesial temporal sclerosis and bitemporal epilepsy are risk factors for DRE in focal epilepsy.[31] The drug resistance risk is higher in patients with cortical dysgenesis or hippocampal atrophy.[32]

## Pharmacological Management

### Alternative Monotherapy or Adjunctive Therapy?

Although polytherapy is frequently used in patients with DRE, few evidences support a significant benefit of adjunctive therapy in comparison with alternative monotherapy. It should however be reminded that all ASDs are first evaluated as adjunctive therapy in Phase III studies conducted in patients with DRE.[33] Accordingly, the level of evidence about the efficacy of available ASDs in the add-on therapy in DRE is high. Rare studies compared efficacy of alternative monotherapy versus adjunctive therapy in patients who had not responded to ASD. In two

studies conducted in Italy, no difference was observed between the two arms.[34,35] However, a large majority of patients included in these studies failed only one monotherapy, and therefore did not fulfil criteria of DRE. Patients were randomized in one study, whereas the other was observational. However, because the randomized study needed to be pragmatic and adapted to clinical practice, no blinding procedure was used. Most importantly, the seizure freedom rate was very different between the two studies, suggesting different patient populations. While remission was observed whatever the treatment strategy in 72% of patients in one study,[35] the 12-month probability of remaining seizure-free was about 15% in the other.[34]

On the other hand, the benefit of polytherapy in comparison with monotherapy has been indirectly shown in other studies, especially when one considers the positive impact of the association of lamotrigine and sodium valproate in patients with DRE[36] or of clobazam with stiripentol of cannabidiol in Dravet Syndrome.[37,38]

However, there are also a large amount of data demonstrating the consequences of ASD-related adverse events on patients' quality of life.[39] In patients with DRE, it has been shown that the negative impact on daily quality of life of ASD-related adverse events is greater than seizure frequency,[40] especially when ASDs alter cognitive functioning, mood or coordination.[41] In this context, reducing ASD load might be beneficial in some patients, though seizure freedom is not achieved.

Overall, the choice between monotherapy and polytherapy should probably vary across patients, depending on types of seizure, seizure frequency, underlying epileptic syndrome and ASD tolerability.

## Choosing ASD Upon Its Efficacy Data in DRE?

As discussed above, one of the main principles is to use ASDs adapted to the patient's epilepsy syndrome. All licensed ASDs, but ethosuximide, stiripentol and cannabidiol, can be used in drug-resistant focal epilepsy. In idiopathic generalized epilepsy as well as in some developmental epileptic encephalopathies,[42] some ASDs should be used with caution, whereas broad-spectrum medications, such as levetiracetam, sodium valproate, topiramate, perampanel, barbiturates or zonisamide, may be preferred.

Beyond this principle, basing the choice of ASD on a hierarchy of efficacy between them is difficult to achieve, both in primary generalized epilepsy[43] and in focal epilepsies.[44] In the absence of head-to-head trials comparing ASDs in DRE, efficacy evaluation relies on indirect comparisons of phase III randomized placebo-controlled trials. Using this approach, no significant difference in efficacy was observed between ASD available in drug-resistant focal epilepsy[44] or in primary generalized epilepsy.[43] Another methodological approach is to compare data of the same randomized studies using network meta-analyses.[45] However, results were similar and mostly showed no statistically significant differences between ASDs for adjunctive therapy.[45] However, all these systematic reviews suffered from similar limitations.[44,45] Because all ASDs are compared to placebo, a key issue is to assume that response to placebo is similar across studies. However, as demonstrated in other diseases, this proved to be wrong. In epilepsy, it has been shown that response to placebo is greater in children than in adults[46] and, in the latter, has progressively increased over the last 20 years.[44] The reasons underlying this evolution are unclear but they are probably multifactorial, including variation in the regression to the mean effect, placebo effect and Hawthorne effect.[44] Whether or not the evolution of how the studies are coordinated, with increased number of study sites and involvement of a very large number of countries in a single trial, has also played a role remains to be determined. However, the validity of comparing placebo-controlled studies performed in the 90s with studies performed more recently is highly debatable.[44]

Another important issue is the primary outcome of the phase III randomized placebo-controlled trials and therefore of their meta-analyses. According to the FDA and the EMA guidelines, the primary outcome of these trials is the decrease of the median monthly seizure frequency or the 50% responder rate (ie, the number of patients who achieve 50% decrease in seizure frequency during the treatment period in comparison with the baseline period), respectively. In contrast, the evaluation of the seizure freedom rate is rarely informative because of methodological issues[47] and because patients included in these studies typically do not achieve period of seizure remission. Accordingly, no difference in seizure freedom rate is usually observed between ASD and placebo.[44] It should however be noted that a recent study evaluating a new ASD, Cenobamate, reported that 21% of patients allocated

to the 400 mg arm were seizure free in comparison with 1% in the placebo group.[48] Although a patient can suffer from different seizure types, the data of phase III randomized placebo-controlled trials are usually informative for only one of them, corresponding to the primary outcome. For instance, patients with drug-resistant focal epilepsy can present focal seizures and focal to bilateral tonic-clonic seizures. However, phase III studies are not designed to evaluate focal to bilateral tonic-clonic seizures.[49] Similarly, studies evaluating ASD in drug-resistant idiopathic generalized epilepsies are typically designed to evaluate tonic-clonic seizures but are less informative for other seizure types, including absence or myoclonic seizures. The same issue has also been raised in epileptic encephalopathies, such as Lennox–Gastaut syndrome.[50]

## Improving Antiseizure Efficacy with Drugs Acting on Disease-Specific Pharmacological Targets?

The primary mechanism of action of the drugs currently available in the treatment of epilepsy can be grouped into five broad categories:[51] (i) Modulation of voltage-gated ion channels, (ii) modulation of neurotransmitter release, (iii) potentiation of GABAergic transmission, (iv) blockade of glutamatergic transmission, and (v) ASD with a different mechanism of action. Apart from few exceptions discussed below, these mechanisms of action share a similar effect on the epileptic networks: through modification of the excitation/inhibition balance, they decrease the excitability of the neuronal network and consequently the risk of seizure initiation or propagation. In contrast, they do not alter the pathophysiological process involved in the epileptogenesis. Accordingly, they can lead to seizure control, but none has showed an antiepileptogenic efficacy[52] and can be considered as a curative treatment of epilepsy.

True disease-specific treatments remain therefore very rare in DRE. A recent review[53] presented patient and etiology-adapted treatments. This approach is attractive but relies on identification of a specific etiology mainly genetic and/or metabolic. Inhibition of the mTOR pathway for the treatment of seizures in Tuberous Sclerosis Complex (TSC) could be considered as the prototypic example. Mutations of TSC1 or TSC2 genes are detected in more than 95% of patients and cause suppression of mTOR (mechanistic target of rapamycin) inhibition, producing an excessive activation of the mTOR signaling pathway and several abnormalities in cell cycle regulation. Beyond decreasing the volume of TSC-related tumors, especially giant astrocytoma or angiomyolipoma, everolimus, a drug inhibiting the mTOR pathway, significantly reduces seizure frequency in patients with TSC.[54] Because of the role of abnormalities in the mTOR pathways of some focal cortical dysplasia,[55,56] antiseizure efficacy of everolimus might not be restricted to tuberous sclerosis,[57] but clinical data are lacking.[58] Few other examples of disease-specific treatments can be discussed. In patients with GLUT1 deficiency, ketogenic diet represents the standard choice because it provides ketone bodies for brain energy metabolism and thus compensates the brain energy failure syndrome caused by impaired glucose transport across brain tissue barriers.[59(p1)] Fenfluramine, a serotonin agonist acting on $5HT_{2B/C}$ receptor, has recently been shown to have a strong antiseizure efficacy in Dravet syndrome,[60] in which preclinical data suggesting involvement of serotonin dysfunction in the pathogenesis of epilepsy in this syndrome.[61–63] In the future, other similar gene-specific therapy might be developed, such as the glutamatergic drug memantine in patients with mutation of GRIN2A gene[64] or drug acting on voltage-gated potassium channels, including Retigabine, in patients with severe epileptic encephalopathies due to mutation of KCNQ genes.[65]

In addition to these few true disease-specific treatments, it has been suggested that some molecules might be used to target epilepsy-related pathological process that might participate to drug-resistance. Drug-resistance might partly be related to overexpression of ABC transporters, especially P-glycoprotein.[66] Verapamil being a competitive inhibitor of ABC transporters,[67] its efficacy an adjunctive treatment to ASD has been evaluated in an open-label pilot study.[68] However, controlled studies are required to formally evaluate its efficacy. The potential interest of diuretics in the treatment of seizures was raised several years ago.[69] It has been reported very often over the last twenty years that during the period of brain development and during epileptogenesis the inhibitory action of GABAergic transmission could be reversed towards an excitatory action.[70] This reversal of the effect of GABAergic transmission would depend on the intracellular accumulation of chlorine linked to a modification of the expression of certain membrane transporters of the latter.[70] Thus, whereas in the adult brain the regulation of chlorine is mainly ensured by the KCC2 transporter, which maintains a low intracellular chlorine

concentration and thus a hyperpolarizing GABAergic transmission, the situation is different in the immature brain and in immature[71] and adult[72] epileptic networks. Indeed, the sodium/potassium/chlorine exchanger NKCC1 is expressed in a pre-dominant manner, favoring the accumulation of intracellular chlorine and consequently modifying the effect of GABAergic transmission towards a depolarizing, potentially pro-epileptogenic action.[70] Because of its antagonistic action on NKCC1, bumetanide could be a pathway for regulating pathological network activity. Despite encouraging animal studies,[73] a therapeutic trial in the management of refractory seizures in neonates failed to show an antiseizure efficacy of bumetanide.[74] However, other NKCC1 antagonists might be developed in the future.[75] Numerous data have shown the importance of the inflammatory reaction during the epileptogenic process.[76] Accordingly, drugs with anti-inflammatory properties and/or targeting the immune system might be of interest in DRE. Blocking the interleukin 1-β pathway has thus been proposed has thus been proposed, using an antagonist of the caspase 1, VX765. Despite interesting data in rodents[77] and in a phase 2a study in patients,[78] the phase 2b trial was stopped because of lack of efficacy. It should however be noted that in several situations, including DRE associated with limbic encephalitis.[79] New Onset Refractory Status Epilepticus (NORSE) or febrile infection-related epilepsy syndrome,[80] anti-inflammatory and/or immunosuppressive drugs must be considered.

## Choosing ASD Upon Their Safety Profile?

It is clear that the factors underlying the ASD choice cannot be limited to efficacy data alone. Safety of ASD can be influenced by several factors: (i) patient's age; (ii) patient's gender; (iii) risk of drug–drug interactions, between ASDs and/or with non-ASD molecules; and (iv) patients' comorbidities.

Risk of drug-related adverse effects varies across patients' age. In children, a specific attention needs to be paid to the impact of ASD on cognitive functioning. Some ASD, including sodium valproate, can aggravate attention deficit,[81] which is very frequent in DRE[82] and associated a greater risk of academic difficulties.[81] Nevertheless, this parameter must also be considered in adults, with particular attention to the elderly. In the later, ASD tolerability might be lower than in young adults because of decrease in drug clearance[83] and/or of greater susceptibility to non-specific central nervous system side effects. The risk of fall and injury is thus greater, especially with ASD associated with increased risk of imbalance, such as sodium-channel blockers,[84] or of impaired alertness, including benzodiazepines.[85]

Another important factor to consider in the elderly is drug–drug interactions, which often lead to the avoidance of enzyme inducers. This issue of drug interaction should also be anticipated regardless of age in the setting of a tumor-related epilepsy where the use of an enzyme-inducing ASD may result in a decrease in the efficacy of the chemotherapy or in women in childbearing age with oral contraception. Furthermore, the long-term association between enzyme inducers and atherosclerosis and risk of cardiovascular events might result in considering limiting the use of enzyme inducers in most patients with DRE, especially in those with additional cardiovascular risk factors.

Anticipating the safety issues related to the risk of malformations and/or cognitive deficit in children after in-utero exposition to ASD is a key rule in women of childbearing age with new-onset epilepsy.[86] This aspect remains mandatory in patients with DRE. Polytherapy has traditionally been considered to be associated with a higher risk of major congenital malformations than monotherapy. However, it has been shown the risks are primarily driven by the type of ASD included as polytherapy than the number of ASDs.[86] As a matter of fact, combination of sodium of valproate or topiramate is an independent risk factor of major congenital malformations.[87]

Lastly, patients' comorbidities must carefully be screened. Without going into an exhaustive list, some frequent examples can be highlighted. Psychiatric comorbidity, either depressive or anxious, is frequent in patients with DRE.[88] Several drugs are associated with a greater risk of psychiatric complications, including levetiracetam, topiramate, zonisamide or perampanel,[89,90] and should be used with cautious in these patients. In contrast, other drugs, such as carbamazepine, lamotrigine or sodium valproate, are approved in the treatment of mood disorders. Some treatments are associated with weight gain and should be avoided in overweight patients. Conversely, others, such as topiramate and zonisamide, are associated with weight loss and should be used with caution in patients with eating disorders. Lamotrigine may cause sleep disturbances or be associated with headache, which is important in the context of frequent migraine comorbidity.

## Using Efficacy and Safety Data to Choose ASD Upon a Rational Polytherapy Approach?

Rational polytherapy has frequently been advocated. It is typically viewed as a way to optimize the efficacy of the association of two ASDs through the complementarity of their mechanisms of action.[91,92] However, as discussed below, this concept might primarily apply to the choice of the most appropriate balance between the expected benefit of the ASDs combination on seizure frequency and the safety profile of the later.

In theory, three situations can be encountered when two drugs are associated: (i) Additive effect, the effect of the association being the addition of each drug apart; (ii) an antagonist or infra-additive effect; or (iii) a synergistic effect corresponding to a supra-additive effect. Synergistic association is the most interesting, but the majority of preclinical and clinical studies are not designed to distinguish synergic, additive or antagonist associations.[51]

A systematic review[93] evaluated published preclinical data with a possible synergistic effect of the association of ASD. A total of 107 studies were included, with a synergistic effect reported in 54%. However, only 65 studies had appropriate methods and only 27 had considered pharmacokinetic intracerebral variations. Accordingly, the majority of preclinical studies were not performed to distinguish synergistic, additive, and antagonistic activities of ASD.[93,94] When restricted to studies with appropriate methods, as many synergic and antagonistic associations were observed, without correlation with the mechanisms of the ASD.[93]

Similarly, no clinical data formally support a synergistic association between ASD. However, rare exceptions must be noticed. The most important is the association of lamotrigine and sodium valproate which proved to be better that combination of lamotrigine with carbamazepine or phenytoin. The value of this association was since reported in other studies.[95] As discussed above, the other exceptions have been reported in Dravet syndrome with association of stiripentol with sodium valproate and clobazam[37] or with association of cannabidiol and clobazam.[38]

However, a key aspect of rational polytherapy is that it should not be only viewed as a way to improve efficacy but also as an important factor for ASD tolerability.[51] Associations of ASDs can favor the occurrence of adverse events.[92] This is particularly true for sodium channel blockers which associations can increase the risk of vertigo, ataxia, diplopia. In a pooled analysis of lacosamide data, the adverse event rate doubled when this ASD was associated another sodium channel blocker compared with association with an ASD with other mechanism of action.[96] Similar observations were reported for association of carbamazepine with lamotrigine.[97]

While in newly diagnosed epilepsy, quality of life primarily associated with complete seizure control, the quality of life of patients suffering from DRE is primarily driven by the occurrence of ASD-related adverse events,[40] especially those affecting mood, cognition and coordination.[41] Anticipating the risk of occurrence of ASD-related adverse events is therefore of paramount importance. Accordingly, limiting the association of ASD with the same mechanism of action may be important.[51]

More generally, in patients who have failed several ASDs, the decision to substitute ASD regimen to another should always be individualized in order to balance at the patient individual level the expected efficacy of the new ASD and its safety profile. Accordingly, a combination might be useful in a given patient but not pertinent in another because the risk of adverse events resulting from her/his comorbidities overcomes the potential benefit of that combination. Maintaining the same ASD regimen despite persistent seizures might thus be the best options in certain patients. However, the benefit in terms of efficacy might vary across seizure types. In patients with frequent tonic-clonic seizures, the risks of seizure-related complications, including the risk of SUDEP,[9] might justify pursuing active treatment revision.

# Non-Pharmacological Management

Every patient with DRE should be referred to a reference tertiary center, especially in the perspective of discussing eligibility for epilepsy surgery or neurostimulation. Despite accumulating evidence about the efficacy of epilepsy surgery and the release of specific guidelines,[98] delay before referring to a tertiary center seems to remain stable, around 15–20 years in North America and Europe.[99]

## Epilepsy Surgery

Epilepsy surgery should primarily be considered in patients with drug-resistant focal epilepsy.[100] There are class I evidences showing superiority of epilepsy surgery over medical management in adults with drug-resistant temporal lobe epilepsy[101,102] and whatever the localization

in children with drug-resistant focal epilepsy.[103] In addition, successful surgery for epilepsy due to early brain lesions despite generalized EEG has been reported in children.[104]

The presurgical evaluation aims to delineate the epileptogenic zone, a benefit/risk balance between resection, disconnection or destruction of a brain region and the minimum neurological deficit.[100] The minimal examination should include interictal scalp EEG, a dedicated MRI protocol for epilepsy, neuropsychological assessment, completed if required by functional neuroimaging.[100] Long-term video-EEG to capture seizures is strongly recommended.[100] Functional MRI is increasingly used to lateralize language and has mainly replaced Wada test in temporal lobe epilepsy.[105] When data at the end of this first phase are not strong enough to delineate the brain region that needs to be resected or if this latter involves eloquent cortex, invasive video-EEG recordings with intracranial electrodes, strips or grids are used.[106] Stereo-electro-encephalography is now the principal method for intracranial EEG monitoring in the majority of epilepsy surgery centers in Europe and in the US.[107]

Overall, seizure freedom following epilepsy surgery is achieved by 60–80% in patients with temporal lobe epilepsy and 40–75% in patients with extra-temporal lobe epilepsy.[100] Moreover, the benefit on quality of life, cognitive evolution, particularly for children, and psychiatric comorbidities is positive.[108–110] This global benefit is also stated in more specific populations, including children with autism spectrum disorders[111] or older adults (more than 60 years).[112] It should be emphasized that lesion on MRI is not a prerequisite for epilepsy surgery.[108] In patients with MRI-negative temporal lobe epilepsy, long-term postoperative seizure-free rates vary from 40% to 60%.[100] Similarly, the presence of a focal MRI abnormality has not been significantly associated with outcome in extra-temporal lobe epilepsy.[113] However, the best results have been reported in focal cortical dysplasia type 2B, with up to 92% of patients achieving seizure freedom after a mean follow-up of 4 years, and no difference between MRI-positive and MRI-negative patients.[114]

Magnetic resonance imaging-guided laser interstitial thermal therapy (MR-guided LiTT) is an alternative to cortical resection. Because of its minimal postoperative morbidity,[115,116] its use is growing in mesial temporal lobe epilepsy. MR-guided LiTT as well as stereo-EEG-guided radiofrequency thermocoagulation might also be useful in patients not eligible for cortical resection including those with periventricular nodular heterotopia or hypothalamic hamartomas. About 50% of patients with periventricular nodular heterotopia can achieve seizure remission following stereo-EEG-guided radiofrequency thermocoagulation.[117]

## Neurostimulation

Neurostimulation can be separated into two groups, vagus nerve stimulation (VNS) and brain stimulation, including Deep Brain Stimulation (DBS) and Responsive neurostimulation (RNS). These approaches showed similar efficacy.[118]

VNS is frequently proposed in patients not eligible for epilepsy surgery. The probability to achieve seizure freedom is low,[119] but there is a positive impact on QOL in 50% of patients.[120] Adverse events are not rare, with intraoperative abnormal heart rhythm, dysphonia, dysphagia, surgical site infection and sleep apnea.[120] Initially validated in focal epilepsy, other studies demonstrated interest of VNS in generalized epilepsies,[119] such as Lennox Gastaut or Dravet syndromes.

DBS proved to decrease seizure frequency in DRE. The highest level of evidence has been reported for stimulation of the anterior nucleus of the thalamus.[121] Long-term study reported 69% reduction in seizure frequency at five years, with two-third of 50% responders.[122] Other targets, including centromedian thalamus nucleus, may also be associated with antiseizure efficacy, especially in Lennox-Gastaut syndrome.[123]

RNS is a closed-loop cortical stimulation device. Cortical strips and/or depth electrodes deliver customized neurostimulation in the seizure onset zone and prevent seizure propagation based on the electrocorticographic detection of abnormalities.[124] In a pivotal double-blind sham-controlled parallel-group RCT which included 191 adult patients with focal DRE, RNS system therapy showed showing an overall 29% responder rate at the end of the double-blind phase and 45% at 2 years in the open-label extension.[125]

## Diets

Ketogenic diet has proven its usefulness in children and adolescents with DRE.[126,127] In adults, the use of ketogenic diet remains uncertain and needs further research. In

case of ketogenic diet, ASD concentrations have to be monitored, due to pharmacokinetic interactions between diet and ASD.[128] A potential beneficial effect of probiotics in DRE has been assessed by a pilot study.[129] Thirty percent of patients with the probiotic mixture for four months experienced for a greater than 50% of seizure reduction, but further investigations are needed.

## Comprehensive Care Adaptations

As mentioned above, the main goals in patients with DRE is to optimize quality of life. QOL determinant in DRE are multifactorial. The relation between seizure frequency and QOL is blurry, some authors showing a statistically significative association,[130–132] whereas others do not.[40] Conversely, poor tolerance of ASD has a negative impact on QOL, adverse events of treatment being a strong prognostic variable for QOL.[40]

Furthermore, the existence of a psychiatric comorbidity – anxiety or depression – is independently associated with QOL alteration.[40,133,134] The burden of epilepsy could also vary according to the type of seizure, given that generalized tonic-clonic seizures, even though less frequent, are associated with more severe seizure-related complications and are associated with increased risk of depression and anxiety.[135] For children and adolescents, a close relation exists between QOL and cognitive impairment, particularly attention deficit.[82,136] In adults, specific data are scarce but point to the same direction,[137] particularly the relation with cognitive impairment and treatment adverse events.[41] In patients older than 50 with drug resistant temporal epilepsy, an impaired cognitive profile (verbal memory performance) was assessed in half of patients by neuropsychological examinations.[138]

A specific period with higher risk for these complications is the transition between adolescence and adulthood. Patients and their families face several issues, including the change from childhood neurologist to adult neurologist. Over the past years, several studies have emphasized the importance of adequately manage this critical period, especially with dedicated transitions clinics in the most difficult situations.[139]

### Psychologic Care

Epilepsy is associated with 2 or 3-fold more psychiatric comorbidities than population and about a third of drug resistant patients are affected by these latter.[88,140] Psychiatric comorbidities include mood disorders, anxiety and some psychotic disorders. Depression prevalence is higher in epileptic population, notably in DRE, and suicide risk is three times higher than the risk in general population.[141] Anxiety comes next,[140] with panic disorder, social phobia, obsessive disorder, generalized anxiety.[142] More than a third of children undergoing epilepsy surgery evaluation reported unmet overall healthcare needs,[143] with greater risk if the patient presented depressive symptoms or with young or unemployed caregivers. In this context, monitoring and care of psychiatric comorbidities is important, especially using dedicated screening scales validated in epilepsy such as the neurological disorders depression inventory for epilepsy (NDDI-E).[144] Importantly, if a specific treatment is needed, epilepsy does not represent a contraindication for antidepressants, with a selective serotonin reuptake inhibitor as a first line.[145] VNS is also approved for refractory depression and might be useful for patients DRE and comorbid depression.[146] Mindfulness therapy is also associated with greater benefits than short-term psychotherapy in QOL, mood, seizure frequency, and verbal memory.[147]

### Cognitive Impairment

Many factors contribute to cognitive impairments in PWE: epilepsy etiology, seizure type, frequency, age of beginning, medical treatment. Moreover, all cognitive functions can be impact to several degrees, such as attention, language, memory, emotions, gestures, executive functions, logic, visuospatial capacities. Given the increased handicap associated with these cognitive difficulties, particularly for formation or professional projects, their early detection is a fundamental element in the ILAE care.[148]

### Education and Professional Impacts

Because occurrence of a seizure at work may expose to a risk of injury, some professional activities are not compatible with DRE. Conversely, some patients suffer from difficulties to achieve their professional objectives not because of seizures per se but because stigmatization. In order to better accompany the patients, several epilepsy centers have created epileptological and occupational physician combined consultations. In children, an individualized host project allows education in ordinary schools or with auxiliary, or adapted education.

## Abbreviations

ABC transporter, adenosine triphosphate binding cassette; ASD, antiseizure drug; CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats; DBS, deep brain stimulation; DRE, drug resistant epilepsy; GABA,

Gamma-aminobutyric acid; GEFS+, Genetic Epilepsy with Febrile Seizures Plus; GGE, genetic generalized epilepsy; ILAE, International League Against Epilepsy; MR-guided LiTT, magnetic resonance imaging-guided laser interstitial thermal therapy; NMDR, N-Methyl-d-aspartic acid receptor; mTOR, Mammalian target of rapamycin; QOL, quality of life; RNS, responsive neurostimulation; SNPs, single nucleotide polymorphisms; SUDEP, sudden unexpected death in epilepsy; TMS, transcranial repetitive stimulation; VNS, vagus nerve stimulation.

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D.G reports has nothing to disclose.

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