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

Transcript from a touchEXPERT OPINIONS

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THE EXPERTS

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INTRODUCTION

Watch three leading experts discuss aspects of the diagnosis and treatment of drug-resistant epilepsy, including the impact of persistent seizures on patients' quality of life, the challenge of treating patients with drug-resistant disease and the latest clinical trials data.

This activity is intended for neurologists and epilepsy specialists in Europe.

LEARNING OBJECTIVES

After watching this touchEXPERT OPINIONS, you should be better able to:

- Recognise the impact of recurrent seizures in patients with drug-resistant epilepsy
- Outline the challenges associated with current standard of care approaches in the management of patients with drug-resistant epilepsy
- Assess how emerging anti-epileptic drugs might address the unmet treatment needs in patients with drug-resistant focal epilepsy

TOPICS DISCUSSED

- Drug-resistant epilepsy: What does it mean for patients?
- Current approaches to drug-resistant epilepsy: Have we reached our goal?
- Optimizing treatment of patients who are drug-resistant: Is seizure freedom a realistic goal?

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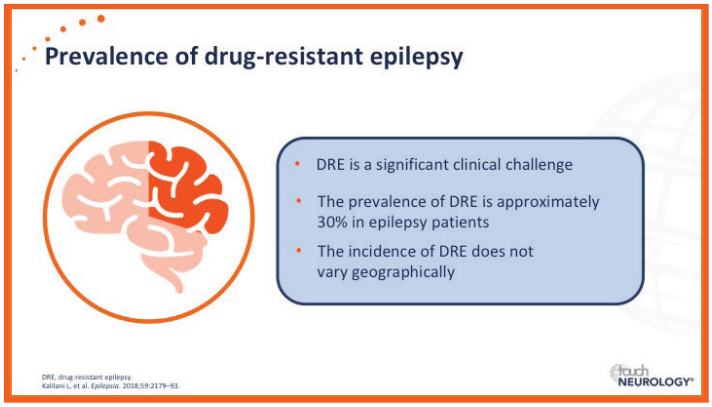
DRUG-RESISTANT EPILEPSY: WHAT DOES IT MEAN FOR PATIENTS?

Dr Christian Brandt

My name is Christian Brandt. I work at Bethel Epilepsy Centre in Bielefeld, Germany, which is a huge, specialized centre for epilepsy and related diseases, and I'm Head of Department of General Epileptology there.

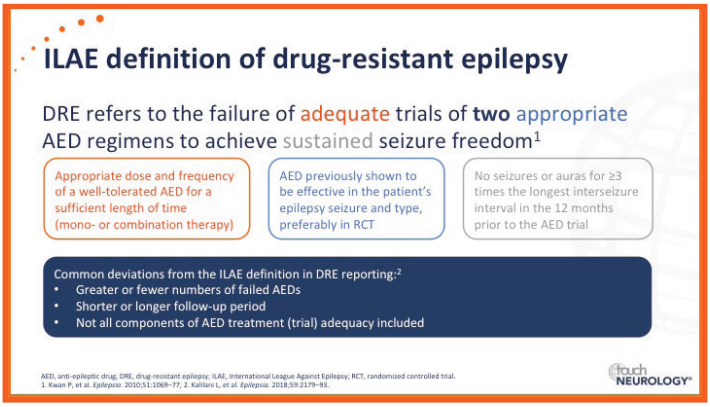
How common is drug-resistant epilepsy?



Drug-resistant epilepsy is very common, and it is a significant clinical challenge. Around 70% of patients with epilepsy will become seizure-free sooner or later and that means, of course, that 30% of patients with epilepsy will continue to have seizures and so they will have drug-resistant epilepsy. You have probably heard about studies showing that you have a very good chance getting the patient seizure-free when you start the first anti-epileptic drug and if the first anti-epileptic drug, the patient is on won't work then there will be a chance with the second drug, and after the second drug the chance of becoming seizure-free will decrease dramatically for the patient.

Well, we have seen around 15-17 new anti-epileptic drugs coming to the market since the early 1990s and the surprising finding is that the number, the percentage, of persons with drug-resistant epilepsy did not decrease significantly after the introduction of these new anti-epileptic drugs. So, you might be interested to hear that the incidence of drug-resistant epilepsy does not vary geographically around the world. And you can see from this that we still need new options to treat our drug-resistant patients.

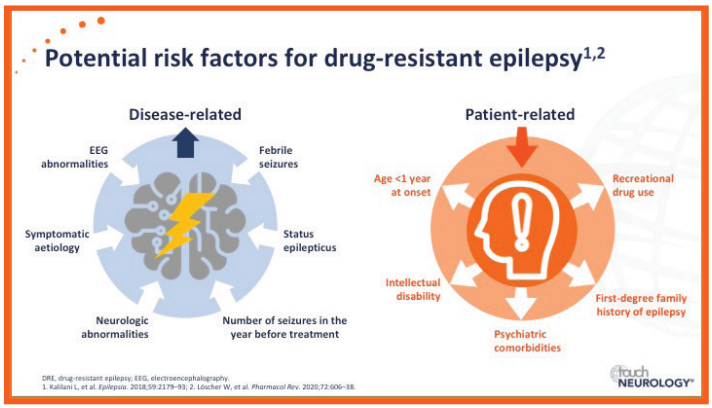
How is drug-resistant epilepsy defined?



The current definition of drug-resistant epilepsy has been coined by a task force of the ILAE, which is the International League Against Epilepsy, and the definition has been published in the year 2010. So, a drug-resistant epilepsy is defined by the failure of any adequate trials of two appropriate anti-epileptic drug regimens to achieve sustained seizure freedom. So, what is an appropriate anti-epileptic drug regimen? It means you have to choose an appropriate anti-epileptic drug. Let me give you an example. If you try to treat a patient with a focal epilepsy with ethosuximide, the drug for generalised epilepsy, then this is not an appropriate anti-epileptic drug. The next thing is, after you've chosen the appropriate anti-epileptic drug you have to adjust to an appropriate dose. If the anti-epileptic drug is under-dosed, then you can't count this as an adequate trial. And, of course, the drug has to be well-tolerated and the observation time has to be long enough to judge the effect.

Another criterion for an appropriate drug is that it has to be previously shown to be effective in the patient's epilepsy and seizure type, preferably in a randomized controlled trial. This is not true for many of the older anti-epileptic drugs but RCTs are, of course, the gold standard in modern epilepsy treatment. And what is sustained seizure freedom? Well, you get a hint that the drug works if no seizures occurred for at least three times the longest inter-seizure interval in the 12 months prior to the anti-epileptic drug trial. But what is most important for the patient is sustained seizure freedom and this is regularly defined by 12 months of seizure freedom.

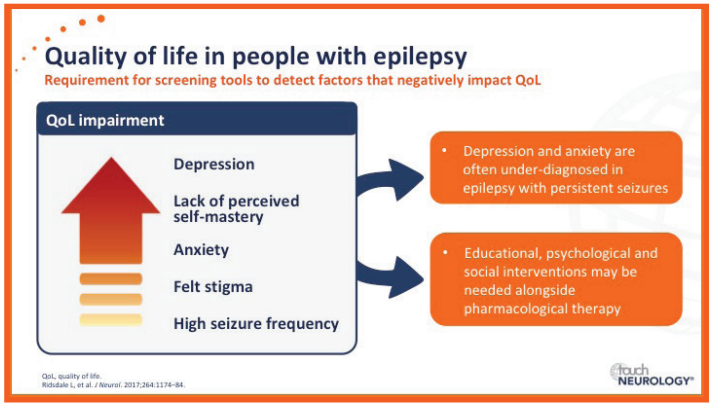
Which factors contribute to drug-resistant epilepsy?



Many risk factors have been identified for drug-resistant epilepsy and this is very important because we can counsel patients about the prognosis of their epilepsy. The risk factors shown on this slide are mainly from a sort of meta-analysis of studies on drug-resistant epilepsy. Not all of these studies used the same definition, but that doesn't matter in terms of the identification of risk factors here. So, let's first have a look at the figure on the left side of the slide. So, febrile seizures are a risk factor for the development of drug-resistant epilepsy, meaning febrile seizures in the patient's history. The occurrence of status epilepticus is a risk factor and also the number of seizures in the year before treatment is a very important one, meaning if someone has a high seizure frequency within the year before treatment that is a risk factor for drug resistance. Neurologic abnormalities, that means findings in the neurological examination or in neuroimaging; and then a symptomatic aetiology as opposed to an idiopathic or cryptogenic aetiology, as it was called in the previous ILAE classification of epilepsy, is a risk factor as well and an abnormal EEG. You can say that these risk factors are disease related and there are patient-related risk factors which are shown on the right side as well. Those are recreational drug use, a first-degree family history of epilepsy and an early epilepsy onset. I would like to draw your attention especially to further risk factors. One is intellectual disability. Persons with intellectual disability constitute a major group among all patients with epilepsy and, as you probably know from your own clinical experience, it is possible to achieve seizure freedom in persons with intellectual disability but the odds are lower as compared to all patients with epilepsy. And another risk factor is if the patient has a psychiatric comorbidity, I want to mention especially depression and anxiety, both contribute to a worse prognosis of the epilepsy.

How do recurrent seizures affect quality of life in patients with drug-resistant epilepsy?

Drug-resistant seizures severely affect the patient's quality of life. You can imagine someone who continues to have seizures may have problems with his driving licence, while there are exceptions that differ from country to country if the seizures persist only during sleep, but in general yes, driving licence is important and is affected by continuing seizures. Patients may have restrictions at work. There is still stigmatisation even in modern society concerning people with epilepsy. And, of course, depending on the seizure type there is also a risk of injury and also especially with continuing and frequent grand mal seizures during sleep there is also a risk of SUDEP, that is sudden unexpected death in epilepsy.



So which factors impair quality of life to a major extent? It's high seizure frequency, it's the stigma the patient feels and then it is some psychosocial factors like anxiety, the lack of perceived self-mastery and depression. Let's go a little bit more into detail with anxiety and depression. So depression and anxiety are often under-diagnosed in epilepsy patients with persistent seizures. There have been many improvements especially with depression in recent years. Anxiety is sometimes called the forgotten comorbidity because it goes even more undiagnosed as compared to depression. So, and as I said when answering the previous question, depression and anxiety contribute themselves to the development of drug-resistant epilepsy and those are modifiable factors. So we have to detect anxiety and depression and the neurologist's everyday life is very busy, so we need screening tools and there are validated screening tools like the NDDIE, which is the Neurological Disorders Depression Inventory in Epilepsy, which has been translated into many languages today. So that means anti-epileptic drug treatment is the main tool for treating epilepsy, but psychosocial interventions may be needed alongside pharmacological therapy. It's always important to remember that epilepsy is a disease with so many faces.

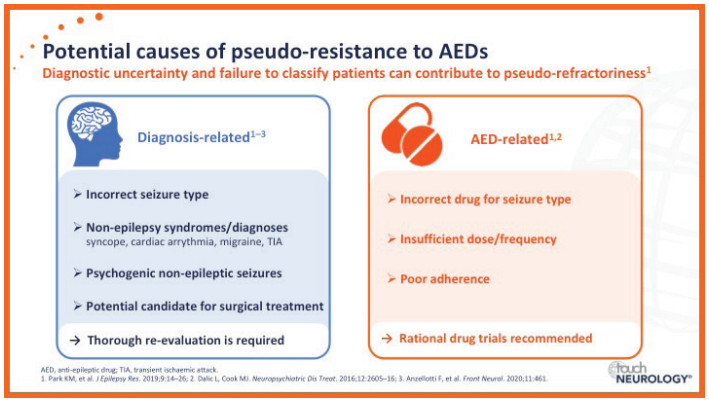
CURRENT APPROACHES TO DRUG-RESISTANT EPILEPSY: HAVE WE REACHED OUR GOAL?

Dr Manuel Toledo

Hello, this is Manuel Toledo. I'm a neurologist/epileptologist in Barcelona, Spain. I'm currently the Head of the Epilepsy Unit in Vall d'Hebron Hospital in the same city, which is a large university hospital here in Barcelona. I am very experienced in the development of different anti-epileptic drugs and in the medical treatment of epilepsy.

What is pseudo-drug resistant epilepsy and why is it important to consider?

Pseudo-drug resistant epilepsy includes patients that still have frequent seizures despite the use of different anti-epileptic drugs. When we say pseudo it's because the treatment is not well adapted to the patients and that can be from the patients' perspective or from the medical perspective and treatment perspective.

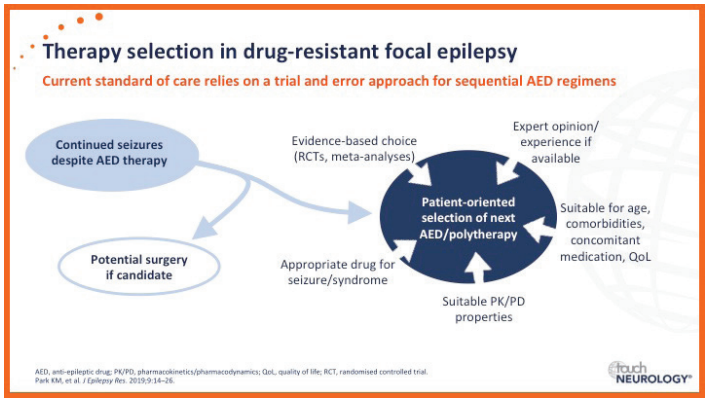


So probably there are some factors which are diagnosis related: incorrect seizure type (rather than incorrect seizure type I would say epileptic syndrome diagnosis is often confused as there is confusion between generalised and focal onset seizures). For some patients with non-epileptic events, psychogenic non-epileptic seizures are probably the most frequent diagnosis, and of course any other type of disorders, the main epileptic disorders. I believe that from the medical treatment point of view, there are aspects related to the drug itself: that it's the incorrect selection of drugs to treat that epileptic syndrome; it's quite often the dosing, so the regular dose that the patient's taking is not enough. Probably one of the main causes of breakthrough seizures and status epilepticus in our population is the insufficient dose of medications.

Also poor adherence occurs quite often because sometimes there is lack of communication or poor communication between doctors and patients and the fact that doctors don't let the patients know that they must take that medication every day to avoid having seizures. So, it's not sufficient to treat the epilepsy, or to treat a particular epileptic seizure in one single day, it's a chronic treatment to prevent recurrent seizures.

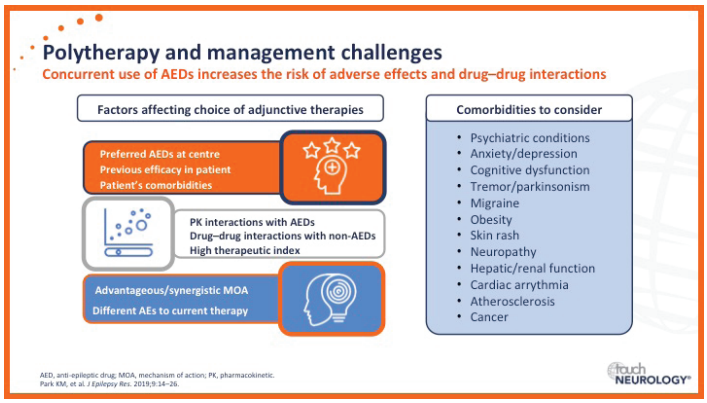
What is the standard of care in true drug-resistant epilepsy?

Well, once we have true drug-resistant epilepsy we double check that the patient is really taking the appropriate medications at the correct doses in the correct posology. So patients who still have seizures when the therapy selection at that point is well defined, and if they are surgical candidates they must go for an evaluation for potential surgery. But the most common scenario is that the patients are not good surgical candidates and at that point it depends on the personal view or the personal experience of the treating physician to make a decision.



I think the challenge with the standard of care, not only on a national, regional, but international level, is knowing what are the therapeutic lines that we need to follow once we have the diagnosis of drug-resistant epilepsy. We know how to treat epilepsy as after the first onset seizure, we know that we have one or two lines of anti-epileptic drugs with different lines of treatments depending on if it is approved or not in that specific country, but then on the third line there is some confusion and then some patients go into surgery, some patients go into medical treatment and the problem is that for medical treatment there is no specific indication for any anti-epileptic drug and it depends on the physician's selection according to the patients' needs to start a different treatment.

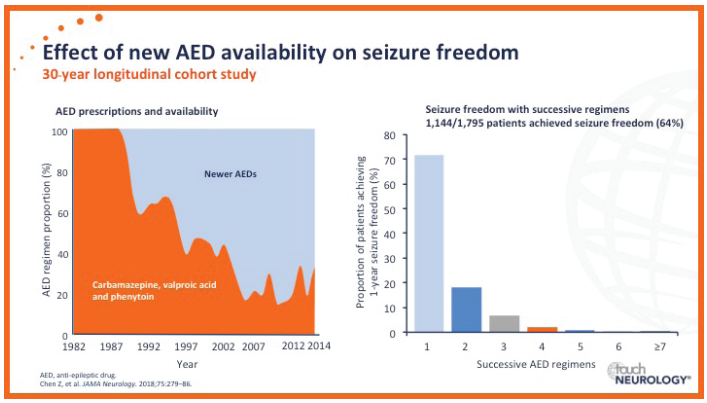
What are the challenges in managing polytherapy in drug-resistant epilepsy?



When we have to select an anti-epileptic drug, we always take into account the first condition, the epileptic syndrome that the patient suffers from and then the comorbidities of the patient. So, depending on whether the patient has any kind of psychiatric disorder, systemic disorder, obesity, etc. And then we select the best anti-epileptic drug according to the comorbidities of the patients to avoid increasing or inducing a worsening of that potential comorbidity. Then it's important to take into account the different anti-epileptic drugs and all the medications that the patient is taking to avoid drug-drug interactions or even pharmacodynamic interactions at some point that may lead to an increase of side effects of the anti-epileptic drug use.

Has the increasing number of available anti-epileptic drugs affected epilepsy outcomes?

Regarding the efficacy of the new anti-epileptic drugs, during the last 10 years there have been more than 10 anti-epileptic drugs launched into the market and the efficacy has been always said to be the same: around 60-70% of patients respond to the first-line therapy. But it's obvious that having epilepsy nowadays is not the same as having epilepsy 40, 30, or 20 years ago, because probably one of the main factors is anti-epileptic drug development. So, we are able to achieve at least as good seizure control as with older anti-epileptic drugs, but obviously with less adverse events and less drug overload. So, we have improved the quality of life of patients a lot, from my perspective at least, as it is difficult to demonstrate that efficacy can improve quality of life according to the results in my daily clinical practice.



So, there are some known factors that predict the response to medical treatment in patients with drug-resistant epilepsy. One of them is the previous use of anti-epileptic drugs. If we move into one, two, three, sometimes four anti-epileptic drugs regimens, probably we have a good opportunity to keep those patients seizure-free. We try to keep a patient seizure-free but after five previous failed trials our probability goes down to zero. Of course there are some other factors such as aetiology, the cause of epilepsy, and the duration of epilepsy itself, but I think one of the factors that we can control is the number of anti-epileptic drugs used by the patient in the past that may predict a lack of response in the future.

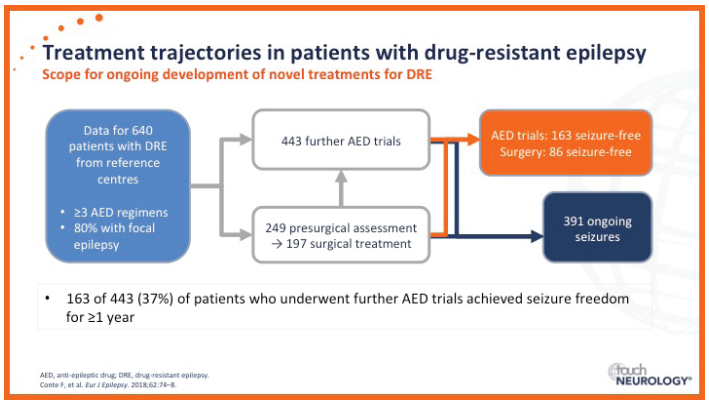
OPTIMIZING TREATMENT OF PATIENTS WHO ARE DRUG-RESISTANT: IS SEIZURE FREEDOM A REALISTIC GOAL?

Prof. Louise Tyvaert

So hello, I'm Louise Tyvaert. I'm Professor in Neurology at the University of Nancy in the east part of France. My medical expertise is epileptology and also clinical neurophysiology and general neurology.

Can patients with drug-resistant epilepsy achieve seizure freedom?

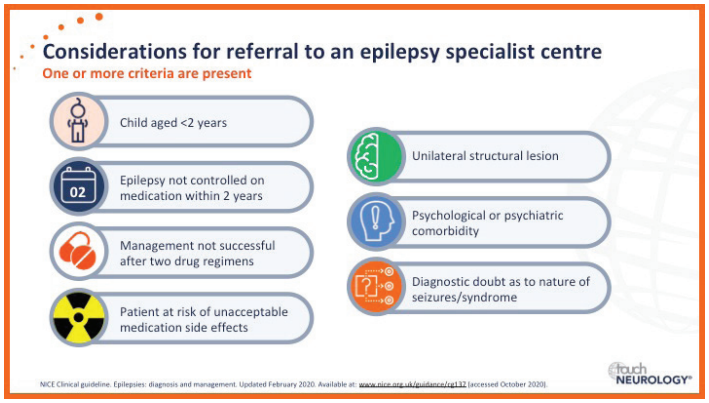
Yes, this is now very well established. Seizure response rate to add-on anti-epileptic drug treatment decreases with subsequent anti-epileptic drug trials. Unfortunately, newer anti-epileptic drugs fail to demonstrate superiority in terms of efficacy compared to older anti-epileptic drug treatments. So, we know that after two failed anti-epileptic drugs trials the chance of becoming seizure-free starts to be very low, but in fact low doesn't mean zero chance.



It is very interesting to read the study of Francesca Conte in *Epilepsia* that collected a database of more than 600 patients with drug-resistant epilepsy, mostly focal epilepsy. The author looks at the long-term outcome of patients undergoing different types of pharmacological or surgical treatments. All of these patients have been already treated with at least three different drug regimens; of those who underwent pre-surgical evaluation less than 200 received surgical treatment. Of the remaining 443 patients not undergoing surgical treatments, but treated only with anti-epileptic drug treatment, 163 patients became seizure-free for more than one year. That means that 37% patients could reach the goal of becoming seizure-free with pharmacological treatment only.

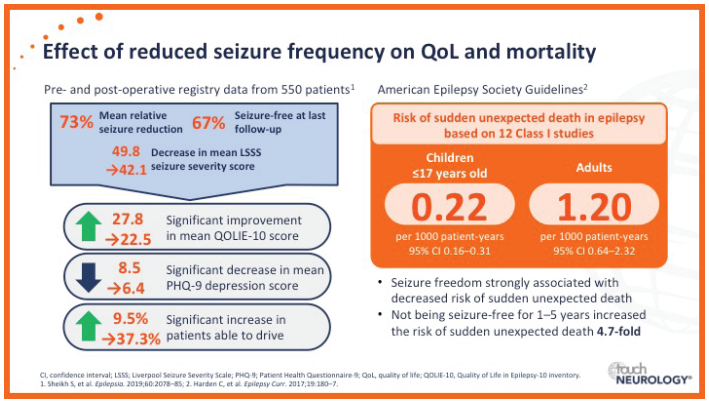
So, clearly there is an important part of drug-resistant epileptic patients who are still susceptible to responding to further anti-epileptic drug trials. Therefore, there is a clear scope for improvement of drug-resistant epileptic patient management: first in defining specific subgroups of patients with a higher chance of becoming seizure-free, and second in developing new treatments.

When should patients be referred to a specialist epilepsy centre?



This is very well defined in the NICE clinical guidelines. They demonstrate that there are clear criteria on which patients should be referred to a specialist epilepsy centre. This is the case when the patient is a child under the age of two years old; when the epilepsy is not controlled on medication within two years; also when management is not successful after two drug results which means the patient is drug-resistant; and also when the patient is at a risk of unacceptable medication side effects; again when the patient has a unilateral structural lesion; as well as psychological and psychiatric comorbidities; and finally when you have a doubt about the diagnosis, either on the seizures or the epileptic syndromes.

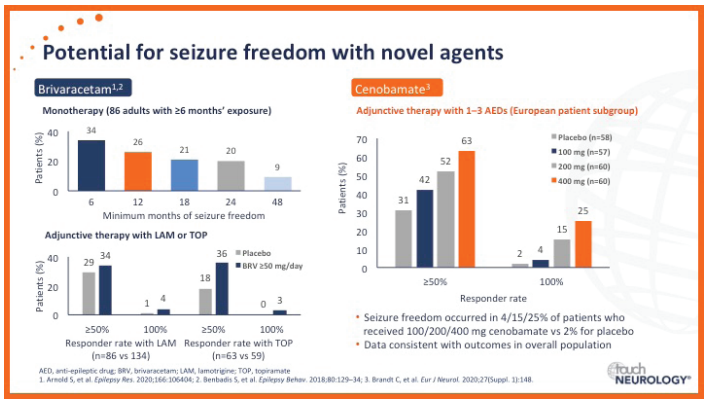
How does seizure freedom affect patients' quality of life and mortality?



So, it is clear that if a drug-resistant epileptic patient should become seizure-free it significantly improves their quality of life. This has been nicely shown in a study by Sheik et al., in *Epilepsia* in 2019. And in this study, they compared the pre-operative and post-operative registry data from 550 patients; among them 67 patients were seizure-free. And in parallel their quality of life was shown to improve based on the QOLIE-10 score, and there is also a clear decrease of the depression score. And an important aspect was to recover the ability to drive; this being one of the major elements to further improvement in the quality of life for these patients. Then to go further, the seizure freedom achieved in these patients with drug-resistant epilepsy will also have a very high impact on their mortality. We all know that the risk of sudden and unexpected deaths or SUDEP in epilepsy is quite high, but when you have drug-resistant epilepsy, this risk is much higher, up to 4.7-fold. And when you achieve seizure freedom this risk is really low. The seizure freedom is truly associated with a decreased risk and this is very important. It means that you have to really target this seizure freedom for those patients to reduce the mortality and also to improve their quality of life.

Do emerging agents increase patients' chances of being seizure-free?

So, as I mentioned earlier, there is scope for ongoing development of novel treatments. While new anti-epileptic drugs introduced over the last decades have better tolerability and drug interactions, they failed to show significant efficacy compared to other anti-epileptic drugs. But there are two recent anti-epileptic drugs that show encouraging data, and on efficacy first, but mostly on seizure freedom achievement in this population of drug-resistant patients.



For example, for brivaracetam, it has been shown that when brivaracetam was used as monotherapy 20% of patients could achieve seizure freedom for more than 6 months. Using brivaracetam as adjunctive therapy could also help to achieve seizure freedom for several more patients.

But in fact, the most encouraging data are those from cenobamate. When you apply cenobamate as adjunctive therapy there is a high number of patients that can achieve this seizure freedom. There are around 25% of patients who were seizure-free with 400 mg of cenobamate. And this rate is really high compared to other drugs trials with a similar placebo effect and this is really, really encouraging. So, I would say for all these reasons neurologists should always consider achievement of seizure freedom as a main target even in drug-resistant epilepsy patients.

What are the clinical implications of recent data on emerging agents for drug-resistant epilepsy?

It is very important that new drugs that may come to the market could offer, first, good tolerability and fewer drug-drug interactions, and second, offer more possibility of combining drugs together with synergistic effect. But also, I think that what is very important, especially with the cenobamate findings here, is that for the first time they offer a seizure-freedom effect which is much higher than with the other drugs. It means that developing new drugs with new pharmacological effects, of combining them together, will probably offer the patient the chance to become seizure-free or at least to have better control of their epilepsy.

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