Epilepsy

Optimising Epilepsy Therapy – Searching for the Evidence – Looking Beyond the Data

Proceedings of a Symposium Presented at the 1st Meeting of the European Academy of Neurology,
22 June 2015, Berlin

Expert reviewed by: Mar Carreño,¹ Eugen Trinka² and Martin Holtkamp³

Abstract
There is now an extensive range of anti-epileptic drugs (AEDs) available including older established treatments and a newer generation of medications. The choice of drugs and what constitutes optimal therapy, however, is unclear due to limitations in the data supporting their use, particularly among the newer treatments. In clinical trials of monotherapy, a treatment is required to show only non-inferiority to another benchmark treatment. In trials of polytherapy, comparisons are limited to placebo. It is therefore necessary to look beyond the study data and consider other parameters to ascertain the most suitable treatment for the individual patient. Available evidence suggests that efficacy is similar among most AEDs, but this does not mean they are all the same. Some show efficacy in early and refractory epilepsy and some improve depression and quality of life (QoL) in epilepsy. AEDs are associated with a range of adverse events (AEs) that can limit their usefulness. AE classifications include type A (augmented and dose related) including tiredness, fatigue, insomnia, dizziness, vertigo, imbalance, ataxia, tremor and cognitive impairment; type B (bizarre and idiosyncratic) including various hypersensitivity reactions; type C (chronic long-term toxicity) including hirsutism, alopecia, weight gain and obesity; and type D (teratogenesis and carcinogenesis). The newer AEDs have been more thoroughly assessed for AEs than older drugs and risks are better understood. In AED safety, it is not better to follow a policy of ‘better the devil you know’ but rather to carefully monitor AE incidence and be prepared to switch drugs to improve tolerability and avoid non-compliance and treatment failure.

Keywords
Anti-epileptic drugs, safety, tolerability, efficacy, monotherapy, polytherapy, clinical trials

Disclosure: Mar Carreño has acted as a paid consultant to UCB, Eisai, Bial, GSK, Medtronic, Shire and Cyberonics. She has received research funding from UCB and Eisai and has received speaker’s honoraria from GSK, Eisai, Bial, UCB, Cyberonics and Shire. Eugen Trinka has acted as a paid consultant to UCB, Eisai, Bial, Medtronic, EVER Neuro Pharma, Biogen-Idec, Takeda and Sunovion. He, or his institution, has received research funding from GSK, Biogen-Idec, Eisai, Novartis, Red Bull, Bayer, and UCB. He has received speaker’s honoraria from GSK, Böhringer Ingelheim, Eisai, Bial, UCB, Cyberonics, and Sanofi-Aventis and is CEO of Neuroconsult GmbH. Martin Holtkamp has received speaker honoraria and/or consultancy fees from Cyberonics, Desitin, Eisai, GSK, Janssen-Cilag, UCB and ViroPharma.

Open Access: This article is published under the Creative Commons Attribution Noncommercial License, which permits any non-commercial use, distribution, adaptation and reproduction provided the original author(s) and source are given appropriate credit.

Acknowledgements: Editorial assistance was provided by James Gilbart at Touch Medical Media and funded by Eisai and Bial. This article reports the proceedings of a sponsored satellite symposium and as such has not been subject to the journal’s usual peer-review process.

Received: 30 July 2015 Published Online: 2 November 2015 Citation: European Neurological Review, 2015;10(2):164–70 http://doi.org/10.17925/ENR.2015.10.02.164

Correspondence: Mar Carreño, Head, Epilepsy Unit, Department of Neurology, Hospital Clinic, Barcelona, Spain. E: MCARRENO@clinic.ub.es

Support: The publication of this article was supported by Eisai and Bial. The views and opinions expressed are those of the authors and not necessarily those of Eisai and Bial. All the speakers received an honorarium fee to talk at the symposium.

Epilepsy is one of the most common serious neurological disorders and has far-reaching consequences, not only for patients living with the condition, but also for their families and society as a whole. It is useful therefore to evaluate whether the advent of newer anti-epileptic drugs (AEDs) has progressed the safety and tolerability of epilepsy therapy. These newer treatments have been designed to overcome some of the safety issues of older treatments that have a major impact on the quality of life (QoL) of people with epilepsy. The newer drugs have been more extensively evaluated in post-marketing surveillance, which has uncovered safety concerns that may not have been apparent during short-term clinical trials. Comparing the efficacy of available AEDs is difficult due to the absence of head-to-head trials. The effective management of epilepsy not only involves controlling seizures, but also other factors such as impact on comorbidities. Real-world studies are important in supporting the efficacy findings of randomised clinical trials, but they have limitations. This article reports a symposium on optimising epilepsy therapy that was convened at the first Congress of the European Academy of Neurology in Berlin in June 2015. The symposium aimed to provide practical advice that could be applied to current daily practice and focussed on how the appropriate AEDs should be chosen, the need to consider the personal circumstances and goals of individual patients during this process.
Efficacy of Old and New AEDs – Are They All the Same?

Martin Holtkamp

Epilepsy-Center Berlin-Brandenburg, Department of Neurology, Charité – Universitätsmedizin Berlin, Germany

**Treatment Concepts in Epilepsy**

The overall aim of epilepsy treatment is to maintain a seizure-free state, enabling patients to lead a normal life with minimal adverse events (AEs) (Figure 1). A poll of the symposium audience found that 48.5% considered efficacy and 48.5% considered safety to be the most important factor in choosing an AED, indicating that both aspects are equally important. Treatments vary according to the type of epilepsy. A prospective trial found that 58% of patients had partial, 23% had generalised and 19% had unclassified epilepsy. Drugs licensed as monotherapy for generalised or partial epilepsy and those that are licensed as add-on therapy for partial epilepsy are given in Table 1. This includes both old and new AEDs and raises the important question, in terms of efficacy, are they all the same?

**Anti-epileptic Drug Monotherapy**

The European Medicines Agency ruled that in regulatory clinical trials, new AEDs for monotherapy should be compared with an optimal current therapy and demonstrate non-inferiority rather than superiority. As an example, a Phase III comparison of controlled-release carbamazepine (CBZ) (up to 600 mg/day) versus zonisamide (ZNS, up to 300 mg/day) (n=456), showed that 84% and 79% of patients, respectively, were seizure-free at 6 months and 75% and 68% at 12 months indicating similar efficacy. This study formed basis of the monotherapy approval of ZNS in Europe.

The UK Standard and New Antiepileptic Drugs (SANAD) study on patients with partial epilepsy compared the effectiveness of multiple AEDs: CBZ, gabapentin (GBP), lamotrigine (LTG), oxcarbazepine (OXC) and Topiramate (TPM) in one of two concurrent pragmatic parallel-group unblinded randomised trials (n=1,721). Over 12 months, in terms of time to treatment failure, LTG was significantly superior to CBZ and OXC, which were significantly superior to GBP and TPM. These differences in effectiveness were maintained over 6 years (log-rank test statistic=22.15, p<0.0001). In terms of tolerability, LTG and GBP were significantly superior to OXC, which was significantly superior to CBZ and TPM.

**Anti-epileptic Drug Polytherapy**

In AED polytherapy studies, patients can receive a standard therapy to which additional doses of test therapy or placebo are added. An example was a Phase III comparison of eslicarbazepine acetate (ESL) (400, 800 or 1,200 mg OD with titration) with placebo in patients receiving one or two concomitant AEDs over a 12-week period. The 1,200 mg dose produced a significant increase in seizure-free patients versus placebo (8 versus 2%, p<0.05) and both the 800 and 1,200 mg doses produced significant increases in responder rates (a reduction in seizure frequency >50%) versus placebo (34% 800mg and 43% 1200mg versus placebo 20%, p<0.05 and p=0.001).

In polytherapy trials, investigations of 12 different AEDs showed widely differing and limited responder rates compared with placebo (20–45% versus 5–20%), and it was not possible to conclude which treatment is most effective. This was due to variability in the study populations and a shortage of head-to-head comparative trials. This lack of clear difference was emphasised in a recent meta-analysis that included data from 40 trials comparing one AED with placebo, two trials comparing two AEDs and one trial comparing two AEDs and placebo. The comparative risk ratios for seizure outcome were determined for eleven different AEDs versus placebo. Whilst there is an increasing trend in median efficacy from LCM to TPM, the 95% credible intervals overlap to the extent that it is not possible to show significant differences in efficacy between the drugs.

A factor that strongly influences the efficacy of AEDs is the number of previous treatments a patient has received. A study on 478 consecutive patients showed seizure-free rates decreased from 62% for patients who had received no previous AEDs to 0% for those who had received seven previous AEDs. In addition, responder rates decreased from 85% to 35% between zero and seven previous treatments. All of these findings suggest that the methods in the regulatory trials used to license AEDs are deficient; they were not reflective of the real world of epilepsy and did not explore the complexities of polytherapy or treatment history. For approval, it is only necessary to know whether the drug is more effective than placebo.

The Retrospective Study of Lacosamide as Early Add-on Along One Year (REALLY) showed that in a group of patients who had one AED failure (n=89), the seizure-free rate was 58% after 12 months compared with 34.3% for patients who had two AED failures (n=110). Respondent rates were 83.0% and 70.4% for the same groups. The Eslicarbazepine acetate in Partial Onset Seizures (EPOS) study was a prospective, multicentre non-interventional trial of 219 patients who were not seizure-free with monotherapy and were given ESL as add-on therapy. Among the patients, 59% had received two previous AEDs, 81% had received three previous AEDs and 19% had received more than three. After 6 months of treatment, 82% of patients were retained on ESL (primary endpoint). The major reasons for discontinuation (n=31, 18%) were an AE (n=22) and lack of efficacy (n=4). In terms of secondary endpoints, 26% and 39% of patients were seizure-free at 3 and 6 months, respectively, and 70% and 82% were responders at 3 and 6 months, respectively (Figure 2).

The retention and responder rates for those receiving concomitant CBZ, levetiracetam (LEV), LTG, or valproic acid (VPA) in this study were not significantly different (75–100% and 70–90%). Although CBZ and ESL are drugs which belong to the same chemical family, this study showed no significant differences.
The World Health Organisation classifies AEs with AEDs. AEDs are divided into five types (Types A–E). This suggests that ESL and the other three drugs. This finding is supported by the Phase III study that compared ESL with placebo as add-on therapy. There was no significant difference in efficacy independently of the patients being concomitantly treated with CBZ or not.

In recent experimental studies, it was shown in hippocampal slices from therapy refractory epilepsy patients, seizure-like activity was largely resistant to CBZ, whereas eslicarbazepine showed potent activity on sodium current recovery from inactivation and discharge behaviour. Moreover, eslicarbazepine displayed add-on effects when applied in addition to CBZ. This data shows that eslicarbazepine retains cellular efficacy in chronic human epilepsy, whereas efficacy of CBZ seems to be lost.

In AED polytherapy, the main determinant of QoL in epilepsy is depression, a comorbidity that occurs in up to 20 % of patients in large community care studies and almost 50 % of patients in tertiary care centres. During a one-year open-label extension of the pivotal Phase III trial of ESL, overall Montgomery–Asberg Depression Rating Scale (MADRS) scores were significantly reduced by 2.0 points (p<0.0001) and Quality of Life in Epilepsy Inventory-31 (QOLIE-31) scores were significantly improved by 3.8 points (p<0.0001). This suggests that ESL has a beneficial effect on depressive symptoms and resultant QoL in addition to seizure control.

In epilepsy, therefore, treatment aims to provide excellent seizure control with minimal AEs. Clinical trials of AEDs do not, however, reflect the real world of epilepsy. The evaluation of AED monotherapy is limited since the design of regulatory clinical trials enables only non-inferiority but not superiority of new drugs to be shown. In trials of AED polytherapy, placebo is used in the comparator arm but inter-drug comparisons are difficult due to the lack of head-to-head trials. The efficacy of AEDs may appear similar but the drugs, however, are not all the same. Evidence from recent studies shows that ESL is effective in patients with early and refractory epilepsy and may be useful in cases of pharmacoresistance to CBZ. Some of the AEDs such as CBZ, LTG and ESL have the added advantage in stabilising or improving depressive symptoms, which have the most detrimental effects on QoL in epilepsy.

### Safety of Old and New AEDs – Better the Devil We Know?

Eugen Trinka

Department of Neurology, Christian Doppler Medical Centre, Paracelsus Medical University, Austria; Centre for Cognitive Neuroscience, Austria

Physicians treating patients with epilepsy all have opinions of the efficacy and safety of the multiple AEDs that are available, but the choice of treatment is often based on personal perception rather than an overall assessment of the evidence. AEDs are divided into ‘old’ types that were introduced from the 1860s to 1980 (bromide to valproate) and the ‘new’ types that were introduced from 1980 to the present (vigabatrin [VGB] to perampanel [PER]). Although AEDs have been available for approximately 150 years, AEs are a substantial cause of treatment failure and seriously diminish the QoL of many patients receiving them. Patients do not tend to report AEs spontaneously, particularly those of sexual dysfunction, or mood disorders. For this reason, it is necessary to actively screen patients using questionnaires or surveys. In seven studies of epilepsy therapy that screened for AEs (n=100–809), AE rates of 27.3–42.7 % were recorded. The World Health Organisation classifies AEs with AEDs into five types (Types A–E).

Type A AEs are augmented or dose-related; these are the most common type, occurring in over 10 % of patients. They can be attributed to known drug mechanisms, tend to occur at the beginning of treatment or after dose escalation, may abate over time and are predictable or reversible. Type A AEs include drowsiness, lethargy,
Optimising Epilepsy Therapy – Searching for the Evidence – Looking Beyond the Data

As a result, open-label and observation discontinue the dose, or modify the dosing scheme (e.g. change to slow release CBZ) to avoid or limit type A AEs. Therefore, it is necessary to titrate at low doses. A study of 1,308 patients with partial onset seizures showed that patients who were titrated from 400mg ESL up to 800mg or 1,200mg reported fewer AEs than those patients who received a starting dose of 800mg (Figure 4).

There are remarkably little data on the cognitive effects of new AEDs. Limited study evidence shows that LTG and LEV cause fewer cognitive effects than CBZ, which has similar effects to phenytoin (PHT). AEDs appear to have the worst cognitive effect profile among these drugs and has produced greater effects in studies compared with LTG and GBP PER has a similar effect on cognitive function to placebo. The new AEDs, therefore, are generally better tolerated than the older AEDs, but there are exceptions to this trend.

The incidence of AEs is also affected by baseline medications when another AED is added. A study of 1,308 patients with partial onset seizures received placebo or 200, 400 or 600mg lacosamide (LCM). AE incidence was greater in those patients who had received a baseline sodium channel blocker compared with those who had received an alternative AED. The rates of these events also increased with greater dose levels of LCM. This effect was also seen in a study that included 797 patients with ≥4 partial-onset seizures per 4 weeks despite treatment with 1–3 AEDs. The safety results were stratified according to the doses of CBZ the patients received (0-800 mg or >800 mg CBZ/day) at baseline prior to switching treatment to placebo or ESL 400, 800 or 1,200 mg/day. Among patients, the incidence of dizziness, diplopia and abnormal coordination was seen to generally increase with rising ESL dose, but this effect was also increased by prior CBZ dose.

Clinical study findings show that measures of QoL is affected to a greater extent by mood and central nervous system (CNS) AEs arising from AED exposure than by seizure frequency. Some AEDs such as ESL improve measures of QoL as was shown in a study (n=255). The overall Mean QoL in Epilepsy Inventory-31 (QOLIE-31) scores after 1 year of treatment were significantly improved over baseline scores (p<0.0001). In addition, most of the mean MADRS scores for depression AEs and QoL were significantly reduced during the same time interval.

To avoid or limit type A AEs, therefore, it is necessary to start at low doses, up-titrate slowly and target the lowest effective maintenance dose. If no improvement is seen in AEs, it is advisable to either reduce, discontinue the dose, or modify the dosing scheme (e.g. change from bid to tid). A better option may be to use a different formulation (e.g. change from immediate release to slow release CBZ).

AED type B AEs are bizarre or idiosyncratic. These are uncommon or rare (<1–0.1 %) and are related to individual vulnerability such as genetic factors but not to dose. These events occur mostly in the first weeks but can occur after years and are unpredictable with high morbidity and mortality and may be irreversible. Type B events include skin rashes, severe mucocutaneous reactions, aplastic anaemia, agranulocytosis, hepatotoxic effects, pancreatitis, angle-closure glaucoma and aseptic meningitis. These idiosyncratic events are hard to predict in trials because they have an incidence of 1/10,000. In order to detect these events with a 95 % probability, a population of 30,000 patients would have to be exposed to the drug, which is impractical. As a result, open-label and observation studies are required in the post-marketing phase; these provide lower level evidence but are important aspects of monitoring drug safety.

Type B reactions also include hypersensitivity reactions such as anti-epileptic drug hypersensitivity syndrome (AHS) and systemic symptoms (DRESS), both of which are associated with 10–20 % mortality. Other hypersensitivity reactions include fever, eosinophilia, arthralgia, organ involvement with skin alterations and drug reaction with eosinophilia. Whilst these reactions are rare (1–2/million/year), they can occur at much higher frequencies if a drug is not properly titrated as was the case with LTG in which reaction rates were as high as 1/200. Hypersensitivity reactions are also associated with age, genetic factors, patient history and radiotherapy and have a potential association with human herpes viruses 4, 6 and 7. Increased hypersensitivity reactions have also been associated with HLA*1502 positivity in a large population of Han Chinese (post-test probability of 26 %) and with HLA-A*3101 negativity among Europeans (post-test probability of 3.8 %). These tests only indicate marginally increased risks, and it is important to determine those patients who have a history of rash prior to treatment.

Both old and new AEDs can cause type B AEs. In a large cohort study of epilepsy patients who were treated with CBZ, LEV, phenobarbital (PB); PHT or VPA, blood dyscrasias occurred in 3–4/100,000 (compared with 1–2/100,000 in the general population). VGB has been associated with visual field defects in 41 % of patients and TPM has been associated with acute angle closure glaucoma (0.6 % after 6 months, 7.41 relative risk in first month). In an estimated population of 6005 patients who received retigabine, 38 (6.3 %) showed skin discoulouration after a median 4.1 years, and 36 had eye examinations. Among these, 11/36 had retinal pigmentary abnormalities, 5 of whom had worse than 20/20 visual acuity and 1 developed retinal dystrophy. In summary, new AEDs may cause surprises in terms of type B AEs, and physicians should look out for them.

To limit the occurrence of type B events, therefore, certain AEDs should be avoided in high-risk groups or used with caution and up-titrate slowly. AEDs causing reactions should be promptly discontinued and symptomatic and supportive care (intravenous immunoglobulins, steroids, etc.) should be given. In addition, new observations should be reported to create new safety signals (pharmacovigilance). Type C AEs are associated with chronic long-term toxicity; they are insidious and common (1–10 %) but develop slowly. They are related to cumulative drug dose and are mostly reversible. These events are mainly associated with older AEDs and include unwanted cosmetic
Epilepsy

Figure 3: Types of Adverse Effects Associated with Anti-epileptic Drugs

Type A: Augmented: dose-related
Type B: Bizarre: idiosyncratic
Type C: Chronic: long-term toxicity
Type D: Teratogenesis and carcinogenesis
Type E: AED Interactions

AED = anti-epileptic drugs Source: derived from Aronson 2002; Perucca and Gilliam 2012.

Figure 4: Adjuvant Eslicarbazepine Acetate in Adults with Partial Onset Seizures – Phase III Pooled Analysis Tolerability According to Dose Titration

Table 1: Dose Distribution

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBO</td>
<td>PBO</td>
<td>PBO</td>
<td>425</td>
</tr>
<tr>
<td>400</td>
<td>400</td>
<td>400</td>
<td>196</td>
</tr>
<tr>
<td>400</td>
<td>400</td>
<td>800</td>
<td>216</td>
</tr>
<tr>
<td>400</td>
<td>800</td>
<td>800</td>
<td>98</td>
</tr>
<tr>
<td>400</td>
<td>800</td>
<td>1200</td>
<td>102</td>
</tr>
<tr>
<td>800</td>
<td>800</td>
<td>800</td>
<td>101</td>
</tr>
<tr>
<td>800</td>
<td>800</td>
<td>1200</td>
<td>308</td>
</tr>
</tbody>
</table>


Epilepsy is associated with sexual dysfunction in up to 30 % of women and 50 % of men. This manifests as loss of libido, erectile dysfunction and anorgasmia. The aetiology of these effects is multifactorial, but they are related to potent enzyme-inducing AEDs. The disease is also associated with osteoporosis, osteopenia and reduced bone density, which are also multifactorial in origin but linked with enzyme-inducing and non-enzyme inducing AEDs. In addition, hypothyroidism has been reported with CBZ and OXC. Patients receiving long-term CBZ, PHT or VPA have also been shown to have altered vascular risk markers (e.g. common carotid artery intima-media thickness) that may accelerate the atherosclerotic process, and this is significantly associated with the duration of AED monotherapy. To limit type C AEs, therefore, it is necessary to avoid long-term therapy, systematically screen patients, and delay treatment (e.g. calcium, vitamin D, folic acid) and discontinue AED if required.

Type D AEs are teratogenesis and carcinogenesis; they are uncommon (0.1–1 %) and are delayed, dose-dependent and irreversible. These can manifest as birth defects, neurodevelopmental delay, pseudolymphoma and brain tumours. Teratogenic effects are associated with prenatal exposure to AEDs, especially in the first trimester when there is a 2–3-fold increase in the risk of major congenital malformations. Polytherapy, high-dose treatment with VPA or PB or a family history also increases the risk of teratogenicity. Teratogenicity is mostly associated with older AEDs, but more data are needed to fully evaluate newer drugs for this risk. Type E AEs are AED interactions; these were not discussed during the symposium.

An additional risk in epilepsy is suicidality, which is largely a consequence of the disease itself. This risk has not been linked with any particular drug, and there is little firm evidence to support such an association. Drugs associated with negative psychotropic effects, however, should be avoided in patients with a history of suicidal tendency.

In summary, AEDs are a complex heterogeneous set of drugs with various CNS and systemic effects. Idiosyncratic effects of AEDs are not predictable, so careful clinical observation and judgement is required. The newer AEDs have been subjected to better pre-clinical and clinical testing than the older drugs, but unexpected AEs may still arise. It is preferable to avoid strong enzyme inducing AEDs and use the newer AEDs, which are not strong inducers. There is a complex interaction between epilepsies, depression and other psychiatric comorbidities, but the risks are becoming more fully understood. Overall, ‘the devil we know’ is not better in treating epilepsy, but systematic screening for AEs and readiness to switch therapies vital to maintain treatment efficacy and QoL.

Voting Results

In post-presentation voting, most attendees (64 %) indicated that the safety profile would be the main reason for choosing a newer AED (Figure 5), but the proportions who thought AEDs have similar or dissimilar efficacy were comparable (29 % versus 33 %). In addition, most thought their choice of AED would now be an evidence-based guideline rather than a clinical experience-based guideline (58 % versus 37 %). The majority of the attendees (69 %) would now routinely screen patients who were receiving potent enzyme inducers (CBZ, PHT, PB) for lipid changes, osteoporosis or sexual dysfunction. The majority (54 %) indicated that efficacy would be the main factor in choosing an older AED.

Discussion and Conclusions

The relative efficacy evaluation of the wide range of AEDs now available has been hampered by regulatory trial designs showing only non-inferiority in the case of monotherapies and comparing only against placebo in the case of polytherapies. There is a lack of direct head-to-head studies to aid treatment choice. Meta-analyses, non-interventional and retrospective studies indicate some variation in seizure control and responder rates of different AEDs, but data ranges overlap, making identification of the most effective treatments impossible. In order to simplify treatment...
Evidence suggests that physicians should not adopt the “better the devil we know” policy and continue to use the same AEDs out of habit, cost limitations or lack of experience. Alternative treatments can offer better safety and tolerability and improve patient QoL. Physicians should monitor safety carefully and be willing to change and tailor therapies to patients’ needs. The AEDs are not all the same, whilst it is difficult to show superiority of any one in terms of efficacy, it is vital to consider other drugs, especially in cases of treatment failure or in patients who have been exposed to multiple previous therapies. As newer AEDs are increasingly accepted and become more widely available, they are likely to increase choice and reduce the serious disease and treatment burdens associated with epilepsy.

Figure 5: Symposium Attendee Responses before and after Symposium Presentations in Response to the Question – If You Now Choose a Newer AED, What Would Be Your Main Reason to Do So?

1. Efficacy 45.8 %
2. Safety profile 45.8 %
3. Habit 63.6 %
4. Simplicity 4.5 %
5. Prefer not to use 4.5 %

Source: Eisai/Blai.

35. Boylan LS, Flint LA, Labovitz DL, et al. Depression but not anxiety is associated with greater experience of newer AEDs in real-world use. The modes of action of AEDs may be more complex than is currently appreciated, enabling similar classes of drug to work additively. The demonstration that seizure control and responder rates decline with increasing treatment number is disturbing and indicates many patients will become increasingly difficult to treat. In the intro experimental findings for ESL are therefore encouraging and indicate that this drug may be effective in cases that are refractory to other treatments.

Evidence suggests that physicians should not adopt the “better the devil we know” policy and continue to use the same AEDs out of choice for the physician, more comparative trials are required, together with greater experience of newer AEDs in real-world use.