THE POSSIBILITIES OF TREATMENT OPTIMIZATION IN DIFFICULT-TO-TREAT ADULT PARTIAL EPILEPSY

Ph.D. theses

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1. INTRODUCTION

The chance of adult-onset partial (mainly temporal lobe) epilepsy patients to reach seizure freedom by pharmacotherapy is about 50%, but 25-30% of them are obliged to suffer seizures even despite surgical epilepsy treatment. The failure of the first antiepileptic drug (AED) heralds future difficulties in treatment. The chance for seizure freedom drops significantly, if two adequately chosen and dosed first-line AEDs given in mono-, or bi-therapy fail. This is internationally considered as "pharmacoresistance" (FR), although recent clinical experience suggests a >15% probability of reaching seizure freedom with antiepileptic pharmacotherapy even is such cases. Those patients poorly responding to antiepileptic treatment and suffering seizures for a long time may develop a chronic and irreversible neuropsychology, psychiatry and psychosocial handicap. They are exposed to antiepileptic side effects and toxicity (e.g. weight gain, sexual dysfunction, cognitive losses) as well as to an increased risk of suicide and sudden unexpected death in epilepsy (SUDEP), underlining the importance of early and effective treatment. The notion of FR does not mean the lack of hope; there are several targets and possibilities to deal with, for improving the patient's clinical state. These means include, for example, improving treatment-adherence, personalised treatment, minimizing the cognitive side effects of AEDs, treating comorbid depression. It may be justified a third AED even after the failure of two AEDs, especially when the mechanisms of antiepileptic actions and the treatment-history are constructively taken into account. One can find treatment-backup in drug-combinations, in better use of the therapeutic potential of the AEDs, in the reduction of polytherapy. The dose-optimization of AEDs has key importance.

2. AIMS

Our main purpose was to examine the possibilities of the optimization of the pharmacotherapy in difficult-to-treat or pharmacoresistant adult partial epilepsy.

Main directions and related studies:

The cognitive effects of first and second generation AEDs;

- **Cognitive sub-capacities relevant in vehicle-driving.**
- **Examination of short-term visuo-spatial and verbal memory.**

<u>Dose optimization of AEDs;</u> the examination of the efficacy of different daily doses of Oxcarbazepine (OXC).

<u>The advantages of combination-therapy;</u> the examination of the efficacy and loss of efficacy of add-on Clobazam (CLB) to Carbamazepine (CBZ).

<u>Inducing a third generation AED with unique mechanism of action;</u>

- **The efficacy of Levetiracetam (LEV).**
- **The efficacy of Lacosamid (LCM).**
- **The predictors of the efficacy of LCM**
- **The selection of AED based on known mechanisms of action; exploring clear treatment-routes in the treatment history of patients.**

3. METHODS

3.1.1. Examination of cognitive sub-capacities relevant in vehicle driving

We included 44 adult (TLE) patients, 26 idiopathic generalised epilepsy (IGE) patients and 26 healthy controls. The diagnosis relied on the 1989 classification system of epilepsies and epilepsy syndromes. In doubtful cases sleep EEG has helped to establish the diagnosis, similarly to the rest of the studies. In these related studies (3.1.1. and 3.1.2.), we involved difficult-to-treat adult epilepsy patients who had a normal brain CT scan (no MRI was available at the time of the study). The AED blood levels immediately before the tests were in the therapeutic range in each case. The included patients had a stable AED treatment for at least half year before the study and had no seizures during the preceding 48 hours. In both study-parts 3.1.1. and 3.1.2., we used the Raven IQ test and the Beck depression inventory (BDI), and for quantifying seizure frequency, we made seizure-weights. We took into account the duration of epilepsy. In study 3.1.1. we also evaluated the anxiety level with Spielberger1 and Spielberger2 self-assessment questionnaires. The Raven IQ of IGE and TLE groups was significantly lower than of the controls ($p<0.05$ and $p<0.001$ respectively); there was no significant difference between the two epilepsy groups. The BDI group-results did not differ significantly; all fell in the normal range.

We used an MST-CARAT tool for testing. This is a computerised device for characterizing the process of acquiring complex movement skills and the stability of

movement-structure in reaction to unexpected relevant peripheral signals. The registrations collected during the tests characterized the most important mental functions involved in vehicle-driving.

The measures of performance:

1. In the assessment phase, the time ratio (per cent) spent by the small quadrant conducted by the test person; outside the automatically moving big quadrant (POT_T)
2. Same in the disturbed phase (POT_D)
3. In the assessment phase, the time ratio (per cent) of the cumulated arm-movement time, spent with joint movement (PXY_T)
4. Same in the disturbed phase (PXY_D)
5. Mean reaction-time to disturbing stimuli (RT)
6. The error-rate of responses to disturbing stimuli (ERR)
7. The time-ratio (percent) of disturbance signals' time (the delay to the correct response+ l sec) spent out, during the disturbed phase (POT_E)
8. The ratio (percent) of the exit-number (the small quadrant leaving the big one) during the disturbed-phase occurring during the time of disturbance-signals (the delay to the correct response+ l sec) (POS_E).

3.1.2. Examination of short-term visuo-spatial and verbal memory

Only those TLE patients with homogenous pharmacology treatment were transferred from study-part 3.1.1., to this part 3.1.2 (n=37). The IGE group was supplemented by four patients (altogether n=30). The number of control persons decreased by two persons (to n=24). For the assessment of the included adult persons, we used interactive computerised tests.

The program-system contained two experiments. In the FCORSI variant, the test person had to reproduce the sequence of the places were the quadrants appear on the screen, while in the VCORSI variant he/she had to reproduce the order of four-letter words. In the presented part of data analysis, the FCORSI and VCORSI performance measure and

its abbreviation is F_HM (V_HM): The mean number of hits in the FCORSI (VCORSI) test (regarding all tests).

For assessing enduring attention, we calculated the number of errors in the choice-reaction-time test.

In study-parts 3.1.1. and 3.1.2. we have statistically analysed the correlation between test results and clinical variables on one hand, and compared the test results of epilepsy patients grouped according to epilepsy-type and treatment, with controls.

We have controlled the normality of continuous variables with Shapiro-Wilk's test. For analysing the correlation of variables, we calculated the correlation coefficient using Pearson's method for normally distributed variables and Spearman's method for not normal ones. For comparing the groups, we used Student's t-test or variance-/covariance analysis for comparing normal variables and we applied non-parametric Wilcoxon- or Kruskal-Wallis tests for not-normal variables. For statistical calculation we used the appropriate tools of statistical analysis system (SAS©) (UNIVARIATE, CORR, NPAR1WAY, REG, TTEST, GLM).

3.2. Examination of the efficacy of different daily doses of Oxcarbazepin

This multicentre, random, placebo-controlled, double blinded study included adult and adolescent (15-65 years) FR partial epilepsy patients. The seizures were classified according to the 1981 International League Against Epilepsy (ILAE) system, the epilepsy diagnosis based on the 1989 classification of epilepsies and epilepsy syndromes. We used the same classifications in studies 3.3 and 3.4. The involved patients had at least four partial seizures during the 8 weeks baseline period before adding on OXC. The antiepileptic treatment (1-3 AEDs) was unchanged during baseline. During the 28 weeks blinded treatment period, on top of their original medication, the patients (n=692) received 600, 1200 or 2400 mg/day of OXC or placebo.

The exclusion criteria were severe relevant medical, psychiatry or progressive neurology conditions; non-compliance; a suicide attempt in the past; drug or alcohol misuse; allergy to CBZ; significant laboratory abnormalities e.g. serum Natrium<130 mmol/L; ongoing treatment with MAO inhibitors, Ethosuximide, Felbamate, or hormonal anti-concipient pills.

The primary measure of treatment efficacy was the reduction of seizure-frequency, based on the detailed seizure-diary kept by the patients (detailing seizure-types). We compared the 28 days baseline seizure-frequency with the mean seizure-frequency experienced during 28 days blinded periods after starting OXC. We considered as responders, who had ≥ 50% reduction of seizure-frequency after the induction of OXC or placebo, compared to the baseline.

We used "multiple testing" Bonferroni method adjusted to Wilcoxon's signed-rank test for comparing the percent changes of seizure-frequencies in groups treated with different doses of OXC or placebo.

3.3. Examination of the efficacy and loss of efficacy of add-on Clobazam to Carbamazepine

We included 55 FR- TLE patients who received adjuvant clobazam (CLB) on top of their ongoing treatment. Those patients who had an AED change within 3 months prior to-, or during the study, were excluded. The only exception was clonazepam (CLN), which we have stopped at starting CLB (40% of patients). When swapping from one drug to the other one, we substituted 1mg CLN-t by 10 mg CLB. We have closely followed the patients for 3-42 months, depending on the treatment-response.

Each patient received with CBZ monotherapy sometime in the past, and despite maximal tolerated dose and „therapeutic" drug serum levels, they had not reached a durable seizure freedom. We added CLB to a CBZ monotherapy in 80%; the rest had used a tri-therapy also containing CBZ; before adding CLB. The daily dose of CLB was 20-40 mg in 77% of patients (in a bi-daily schedule). We had reached this dose gradually, in a week's time.

The inclusion criteria of this (3.3.) and of study 3.4 studies were the followings: a clear diagnosis of epilepsy, good compliance, a detailed seizure-diary kept during the preceding 3 months before inclusion and during the study (specifying seizure-types and severities).The exclusion criteria of this study (3.3) and of studies 3.4 were the followings: psychogenic seizures, progressive brain damage, severe medical (liver- or kidney failure, heart, vascular or gastrointestinal conditions), alcohol or drug misuse or psychotic episode necessitating hospitalisation, treatment with additional psychoactive drugs and an IQ<50. Before inclusion and at the end of the follow-up period in each study (3.3., 3.4.1., 3.4.2.),

basic laboratory blood-checks and - where appropriate -, serum drug level tests were performed, and no relevant drug-level changes influencing seizure-frequency, were allowed.

The main measure of efficacy was the change of seizure-frequency based on seizure-diaries kept by the patient. We compared mean seizure frequencies for 12 weeks periods before and after starting the new drug. Our schedule was the same in study 4. The monitoring of seizure-frequency was especially close (at least once in every two weeks) during the first three months after starting CLB. We considered as improvement a 25-75% decrease of seizure-frequency. We assessed the incidence of secondarily generalised tonic-clonic seizures separately.

We considered as tolerance the partial or total loss of CLB therapeutic efficacy; signalled by the recurrence of seizures; compared to an earlier improvement. We compared the clinical data of those patients (n=6) with full tolerance developing within 2.5 months with the ones with no tolerance (n=14). We used BMDP statistical program-package, Paired-Samples t-test and discrimination analysis for the statistical evaluation of data.

3.4.1. Examination of the efficacy of Levetiracetam

In the frameworks of the first Hungarian study on LEV, we performed a retrospective study on 55 FR epilepsy patients followed up in our clinic. The basis of the study was the outpatient documentation of the patients. The inclusion and exclusion criteria were the same as in studies 3.3. We excluded also those patients with a treatment-change within 3 months before or at the start of LEV or during the follow-up period. We applied this same additional exclusion criterion in study 3.4.2.

We divided the patients to seizure free, improved (≥ 50% reduction of seizure frequency), unchanged (ineffective) and increased seizure frequency groups, based on the detailed and reliable seizure diary kept by the patients. We followed up our LEV-patients for 6-39 months; dividing them to three groups based on clinical and pharmacotherapy data. Most patients (n=30) had partial-, mainly temporal lobe epilepsy. These persons could not reach endurable seizure freedom previously neither with two AEDs in monotherapy nor with a bitherapy. The average daily LEV dose in this group was 1950 mg (range 1000- 3000

mg). In the study-population, there were 9 IGE patients and 16 patients with malignant of maligned epilepsy syndromes.

3.4.2. Examination of the efficacy of Lacosamide

In the first phase of this study, we included 43 adult, FR patients, who had started LCM earlier. The inclusion and exclusion criteria were the same as in study 3. We used the care-data of one single epileptologist. Depending on the therapeutic response to LCM, we followed up the patients for 3-65 months. The study group consisted mainly of TLE patients, treated earlier with ≥3 AEDs (in monotherapy or combination) without reaching an endurable seizure freedom. Each patient suffered in complex partial seizures, some of them in secondarily generalised tonic-clonic seizures as well. The mean daily dose of LCM was 305 mg (range 100-400); the up-titration speed was 100 mg/week in each case.
Twenty-two of the 43 included patients had received a "traditional" Na-blocker.
We defined "improvement" as ≥ 50% reduction of seizure frequency, and we have not stated an improvement, irrespectively of seizure frequency, in cases where generalised tonic-clonic seizures persisted.

3.4.2.1. Examination of the predictors of Lacosamide-efficacy

In the second phase of this study, we have looked for a correlation between the efficacy of LCM and the data on the patients' antiepileptic drug-histories.
For evaluating the possible correlation, we have re-selected our patients using strict criteria, aiming also to decrease the distortional effects of the retrospective analysis.
We set two small patient-groups. The first one included patients (n=10) with long (≥12 months) seizure freedom or lasting improvement (≥50% decrease of seizure frequency); and the second group included patients (n=9) improving just transitorily (<6 months) or not at all. These were the inclusion criteria to the groups „successful LCM treatment" and „failed LCM treatment" (groups 1. and 2. respectively), on top of the basic ones. The patients had kept a detailed seizure diary during the whole treatment-period before starting LCM and the epilepsy specialist in charge, had closely and continuously monitored seizure-frequency during the whole treatment period. All patients had an MRI brain scan with epilepsy protocol, and those patients who had epilepsy surgery within 10 years before the study, have been excluded.

In the two patient-groups, we have individually, one-by one in each patients, analysed the experiences with previously administered AEDs; based on good quality and detailed care data. Depending on the date of the first patient-visit and from the time-log since FR could be diagnosed, we have followed back the treatment-history of our patients for 2-10 years before starting LCM. We ordered the previous treatment experiences into four categories: seizure freedom for ≥ 6 months; improvement (≥ 50% reduction of seizure-frequency) for ≥ 6 months; lack of effect; and worsening. The analysed AEDs were induced on top of-, or in place of the earlier, ineffective AED. We took into account also those AEDs, which had to be cut down for side effects.

Finally, we have compared the two groups' mean age, retrospective follow-up period, epilepsy duration, seizure frequency and the number of the tried AEDs during treatment-history.

3.4.3. Exploring and analysing clear treatment-routes in the treatment history of patients

For fulfilling our aims we used database of the LEV study (3.4.1, published in 2007) and the LCM study (3.4.2.1., published in 2015, see above).The inclusion criteria were identical with those in the LCM (3.4.2.1.) study, and the exclusion criteria were the same as in the CLB (3.3.) study. We excluded those patients who had epilepsy-surgery during the analysed period. The included patients' first AED at the beginning of their treatment history was CBZ, and they all had been treated with the highest tolerable dose of the analysed AEDs before a swap to another AED became necessary.

Each patient of group-l (n=8) improved on CBZ (CBZ+ group), while the patients of group-2 (n=14) had not (CBZ- group). "Improvement" with an AED was defined as seizure freedom for ≥ 6 months or ≥ 50% reduction of seizure frequency. We have not stated an improvement, irrespectively of seizure frequency, in cases where generalised tonic-clonic seizures persisted. We have analysed the drug treatment histories of the 22 patients, and we have individually analysed the efficacy of the used AEDs, going back for 2-10 years. The analysed AEDs were induced on top of-, or in place of the earlier, ineffective AED. Based on our retrospective analysis, we have positioned the most often-used CBZ, LEV, topiramate (TPM) and LCM, in the long-term process of drug treatment.

Finally, we compared the variables of the CBZ+ and CBZ- groups in accordance with the LCM (3.4.2.1.) study. For statistical analysis in the LCM study (3.4.2.1.) and in the present (3.4.3.) study, we controlled the distribution of variables using Shapiro-Wilk test, and we chose the adequate statistical probe after. We used Mann-Whitney U-test and paired sample t-test depending on the actual distributions.

4. RESULTS

4.1.1. Examination of cognitive sub-capacities relevant in vehicle-driving.

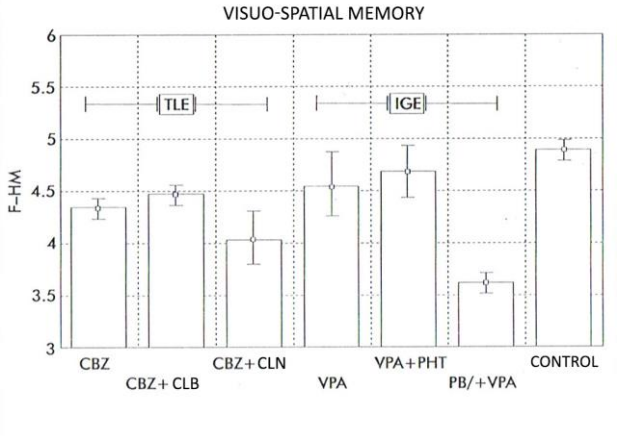
Because of the weakness of correlation between clinical variables and test-results, we disregarded the effect of clinical variables and we compared the groups by MST-CARAT performances.

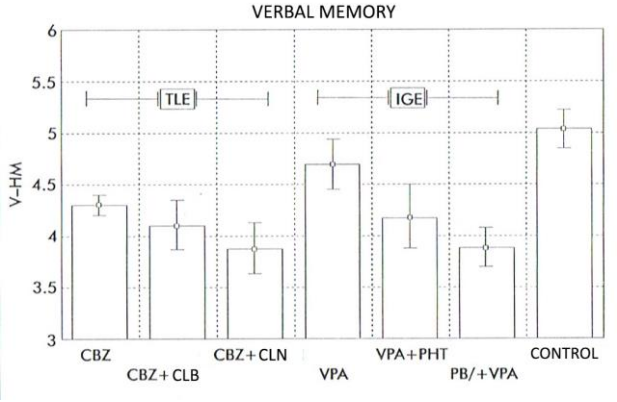
The performance of IGE patients fell behind controls in POT_T ($p=0.0404$); while TLE patients performed less than controls in POT_T, POT_D and PXY_T ($p=0.0002$, $p=0.0003$, $p=0.0001$ respectively). The IGE patients on VPA monotherapy have not performed poorer in any test than controls, while the non-monotherapy IGE group fell behind controls in POT_T ($p=0.0116$). Both CBZ monotherapy ($n=16$) and non-monotherapy ($n=28$) TLE patients performed significantly poorer than controls in POT_T, POT_D and PXY_T. In the monotherapy group these differences were smaller ($p=0.0116$, $p=0.0034$, and $p=0.0068$ respectively) than in the non-monotherapy group ($p=0.0003$, $p=0.0001$, $p=0.0008$ respectively). The patients treated with Phenobarbitone (PB) (7 IGE and 3 TLE patients of the non-monotherapy group) had significantly ($p=0.0139$) poorer performance in POT_T than the rest of all patients.

4.1.2. Examination of short-term visuo-spatial and verbal memory.

In variables F_HM and V_HM, the performances of TLE patients ($p<0.001$), and the performances of IGE patients ($p<0.05$) were poorer compared to controls.

Regarding homogenous drug-treatment groups of patients, the IGE group treated with PB (IGE-PB) (n=8) performed the most poorly: in the spatial memory task (F_HM) their performance was significantly ($p<0.05$) less, compared to all groups, apart from the TLE-CBZ+CLN group (n=7) only. In this variable, the IGE-PB group was significantly ($p<0.001$) weaker than controls. TLE patients treated with a CBZ monotherapy (TLE-CBZ) (n=19) performed in F_HM poorer ($p<0.05$) than controls, too. In V_HM, the IGE-PB group fell significantly ($p<0.01$) behind controls; while the TLE-CBZ and the TLE-CBZ+CLN groups' performances were also weaker ($p<0.05$) than controls. The TLE-CBZ+CLB (n=11) and the IGE- VPA+PHT (n=9) groups have not performed poorer compared to controls.





Analysing the potential memory-effect of AEDs we also explored the effects of the epilepsy itself, the type of epilepsy (IGE-TLE difference) and the side of TLE focus in changing memory performances.

We have chosen statistical models and methods for eliminating the disturbing effects of basic variables.

Question 1: Is the performance of epilepsy-groups lower compared to controls?

For studying this question, we included those epileptic patients on CBZ and VPA monotherapy. Based on our analysis we could find that the spatial memory-performance (F_HM) correlated with the IQ (r=0.59) and the deficit of attention (r=0.46), while verbal memory-performance (V_HM) correlated significantly (r=0.36) just with the IQ. We compared the groups' (F_HM) memory performances, simultaneously eliminating the disturbing factors, using 2-tailed analysis of variance (ANOVA). The differences found in spatial memory-performance were well characterized by the chosen model (explained variance 55%). The strongest factor was found to be the IQ, i.e. it influenced the spatial memory the most strongly. After eliminating additional factors, the study groups did not differ significantly in F_HM.

The model of verbal memory performances has shown a statistically significant value (explained variance 27%); we found no group-effect just the tendency of IQ effect. Deducting it, the difference between TLE and control has remained significant.

Question 2: Is there a difference between the TLE and IGE groups on monotherapies?

We found that spatial memory performances had equal weak correlations with the IQ, the parameter of the deficit of attention and seizure-frequency; while the verbal performance-excluding the control group – did not correlate with any basic variables .

The differences of spatial memory performances were well explained by our model (explained variance 49%). There was no significant group effect (TLE versus IGE). Analysing the verbal memory performance our model has not reached, just approached the statistical significance (explained variance just 10%). Because in this model there were no additional factors besides group effect, the (tendency-like) memory-difference found, could be attributed to the type of epilepsy.

Question 3: Is there a correlation between the side of the epilepsy focus and the memory performances in TLE?

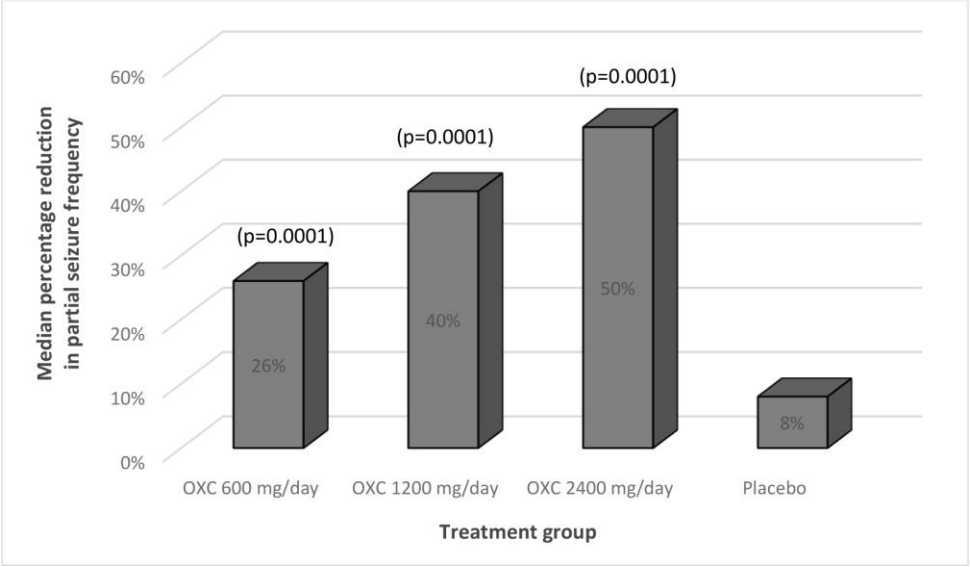
In our analysed TLE group, there were 9 patients with a probable left-, and 7 patients with a right sided focus. Because in this group none of the basic variables correlated with memory performances, there was no disturbing effect to take into account during the

analysis of variance. There was no difference of memory performance between right and left TLE patients /mean F_HM: 4.21 (standard deviation -sd-: 0.71) versus 4.32 (sd 0.49) p=0.7381; V_HM: 4.19 (sd 0.48) versus 4.24 (sd 0.49) p=0.8758/.

Question 4: Do AEDs have an impact on the memory-differences of patients?

First we performed correlation analysis in the 6 treatment groups as above, for identifying the potentially disturbing basic variables. Spatial memory performance (F_HM) had a week statistical correlation with IQ, attention-disturbance and seizure frequency, while verbal memory performance has weakly but significantly correlated with attention disturbance only. The analysis of variance model has well explained the differences in spatial memory performances (explained variance 51%), but beside the determining effect of the IQ and the disturbance of attention has not shown any significant drug effect. The model describing the effects on verbal memory performances has just approached the statistically significant level, but none of the variables could explain the difference.

4.2. Examination of the efficacy of different daily doses of Oxcarbazepin

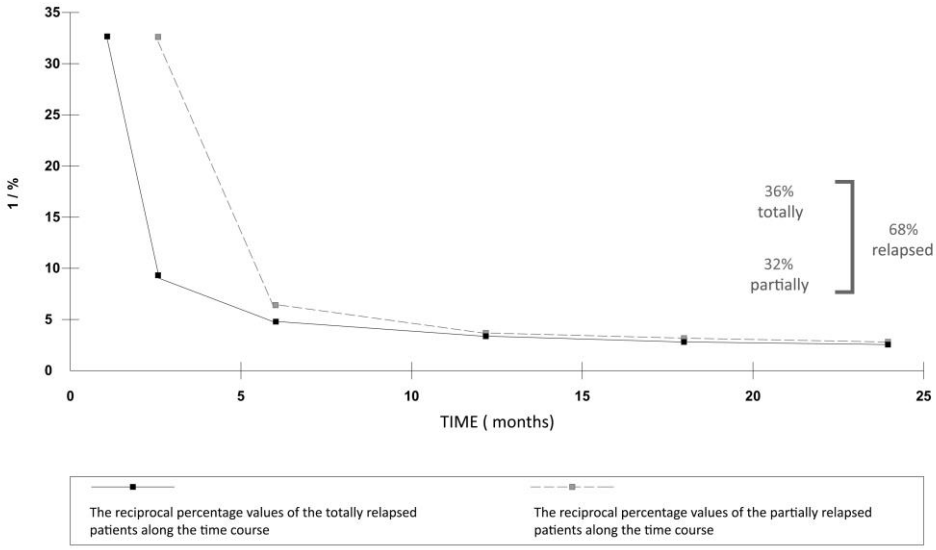


The median value of the decrease in seizure frequency was 26% at 600 mg daily OXC; 40% at 1200 mg and 50% at 2400 mg, while it was 8% at placebo (comparing any dose of OXC with placebo, p=0.0001). The percent ratio of responders (≥ 50% decrease in seizure frequency) was 27% at dose 600 mg; 41% at dose 1200 mg, 50% at dose 2400 mg, while

it was 13% on placebo (comparing OXC groups with placebo, p=0.0008, p=0.0001 and p=0.0001 respectively). The median decrease of secondarily generalised seizures was 71% at 600 mg daily OXC; 86% at 1200 mg and 94% at 2400 mg, while it was 12.5 (p=0.0001 comparing any OXC dose's effect with placebo). The number of adverse drug effects has dose-dependently increased (600 mg/day 83.9%; 1200 mg/day 90.4%; 2400 mg/day 97.7%). The incidence of early dropout from the study due to adverse drug effect was 8.7% in the placebo group and 11.9, 36.2 and 66.7% in the 600 mg, 1200 mg and 2400mg daily OXC groups respectively. Eighty point five percent of these dropouts have occurred within 3 weeks after starting the study drug.

4.3. Examination of the efficacy and loss of efficacy of add-on Clobazam to Carbamazepine.

In the end of the first month after inducing CLB, 71% of patients were seizure free, 20% of them have improved; 3% have relapsed after a transitory improvement and 6% have not responded to treatment at all. After 2.5 months, 64% of patients was seizure free and additional 16% have remained in an improved state. In 6 months' time, 42% of patients were seizure free and 16% have improved. In 24 months' time 15% were seizure free, and



11% have remained in the improved state; 36% of them have fully relapsed, and 32% have relapsed partly. No further loss of efficacy of CLB was seen later. Thirty-three patients had secondarily generalised seizures; which have ceased in eleven of them during the follow-up period.

Swapping from CLN to CLB has resulted in a durable improvement in 40% of patients.

In those patients with a rapid and full relapse, there were more frequent temporal spikes on the EEG before starting CLB, compared to those with no tolerance ($p<0.05$), and there were no additional significant differences between the two groups regarding the rest of clinical parameters taken into account. There was a 29% rate of adverse events.

4.4.1 Examination of the efficacy of Levetiracetam

Sixteen percent of the 30 partial epilepsy patients developed a durable seizure freedom; 33% of them improved for a long-term. Two patients have fully relapsed after 4 and 6 months' freedom of seizures; LEV had no effect in 40% and a paradoxical effect (increase in seizure frequency) occurred in one patient. In the end of the study, 18 patients (60%) have remained on LEV treatment, 6 of them in monotherapy. LEV has remained effective in this group for the long term, apart from one patient. There was a 17% rate of side effects, but none of them needed stopping the drug.

No seizure freedom could be reached in the malignant or malignised heterogeneous epilepsy syndromes' group; 37% of the 16 patients have improved permanently. Seven patients (77%) from the IGE group have become permanently seizure free.

4.4.2. Examination of the efficacy of Lacosamide

After starting LCM, 6 (14%) of the 43 patients became durably (during the whole follow up period) seizure free. There was a long-term (≥12 months) improvement in 11 patients (25%), and the easing of complex partial seizures could also be observed in some cases. The improvement was transitory (<6 months) in 11 patients, and the treatment was unsuccessful in 2 of them. At the closing point of data monitoring, 23 patients (53%) were on LCM treatment. There was a 35% rate of side effects, 11 of the 15 patients have received a “traditional” sodium-channel blocker drug as well.

4.4.2.1. Examination of the predictors of Lacosamide-efficacy

Previous treatment-experiences in a group of selected patients successfully (for at least 6 months) treated with LCM earlier, have shown that the “traditional” sodium-channel blockers CBZ or OXC used to be similarly successful, while LEV was ineffective or caused deterioration in each case of this group. In selected patients unsuccessfully treated with LCM, CBZ or OXC used to be ineffective earlier in each case as well.

Comparing these two groups using a two-tailed t-test regarding the number of AEDs which were tried during their treatment history, we have found a significantly (df=15; p=0.018) higher number of drugs in those patients unsuccesful with LCM. We interpreted this result so, that this LCM-negative group contained patients with more serious FR.

4.4.3. Exploring and analysing clear treatment-routes in the treatment history of patients.

Our study allowed identifying two clear treatment routes. In the beginning of the first one, CBZ had resulted in a transitory (at least 6 months) „improvement” (group 'CBZ+'). This was followed by an ineffective LEV treatment (besides additional unsuccessful trials), and in the end of the route which is the starting point of the retrospective study, LCM has brought improvement again. In the beginning of the second route CBZ used to be ineffective (besides several additional drugs) (group 'CBZ-'). This way has than diverged: on one branch, LEV was ineffective but TPM has helped, on the other branch, LEV has resulted in an improvement. In group 'CBZ-' LCM administered in a late phase, has been ineffective in each case.

Regarding the number of AEDs tried during treatment-history, there were significantly less (F: 25.11; df:1; p<0001) trials in group 'CBZ+' compared to group 'CBZ-'. The most frequent drug-combinations was valproate/lamotrigine (10 cases). This combination has resulted in an improvement in two cases in the group 'CBZ+' and 'CBZ-' each.

5. CONCLUSIONS

5.1.1. Examination of cognitive sub-capacities relevant in vehicle driving

Based on our study performed with a computerised device, the cognitive sub-capacities relevant in the vehicle driving of TLE patients (especially on no CBZ monotherapy) and those patients treated with PB have fallen behind healthy controls. In the case of these patients, evaluating the aptitude for vehicle driving has to involve neuropsychology aspects as well.

5.1.2. The examination of short-term visuo-spatial and verbal memory

We concluded based on our study results that the first and second generation AEDs do generally not have a considerable effect on short-term memory performance. A good seizure control (therapeutic blood levels of drugs in mono-, or bi-therapy) seems more important in view of memory performances than the type of the actual AEDs used.

5.2. Examination of the efficacy of different daily doses of Oxcarbazepine

Based on our study results, just high doses of adjunctive OXC are effective in some of the FR partial epilepsy patients. The relation of the risk of adverse effects versus efficacy may better be adjusted in clinical circumstances provided by higher doses. This study highlights the importance of dose optimization in this patient group.

5.3. Examination of the efficacy and loss of efficacy of add-on Clobazam to Carbamazepine

Based on our study, the combination of CBZ+CLB in the treatment of FR- TLE is highly favourable, because 42% of patients were seizure fee even after 6 months, and 15% of them has remained free of seizures on the long term. At the same time, our results suggest that the issue of the loss of effect is not over-estimated in case of CLB; 36% of patients have relapsed within 24 months fully, and 32% have relapsed. We did not find a cross tolerance between CLB and CLN. Due to its rapid and outstanding efficacy CLB may be a very useful drug during short-term treatments (drug-changes, catamenial seizures).

5.4.1. Examination of the efficacy of Levetiracetam

Based on or study, the adjunctive or monotherapeutic use of the broad-spectrum LEV is an effective and safe AED in 50% of patients on the long term. Sixteen percent of patients has become durably seizure free as well. None of the patients in the study had to

fully stop LEV for side effects. The side effects associated to lack of efficacy in 50% of cases.

5.4.2. Examination of the efficacy of Lacosamide

Based on the first part of this study, adjunctive LCM was an effective and safe AED in about 40% of our FR partial epilepsy patients. It has reached a durable seizure freedom in 14% of patients. None of the patients in the study had to fully stop LCM for side effects. The side effects were more frequent with combination of "traditional" sodium-channel blocker drugs, however, the worst tolerability has not associated to less efficacy.

5.4.2.1. Examination of the predictors of Lacosamide-efficacy

In FR partial epilepsy, the success of LCM- stimulating slow inactivation of voltage-gated sodium channels – can be expected in relatively easier-to-treat patients, who had improved earlier to "traditional"- blocking fast inactivation of voltage-gated sodium channels- AEDs.

5.4.3. Exploring and analysing clear drug treatment-routes in the treatment history of patients

Based on the 2-10 years exploration of treatment routes, the difficult-to-treat patients unresponsive to CBZ, LEV and TPM may still succeed even after 2-5 AEDs. The explored followable treatment routes highlight the importance of known mechanisms of AED action in the long-term treatment of patients.

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