



Outcome Of Medical Treatment In Patients With Drug-Resistant Epilepsy

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Abstract

Background: Epilepsy is a major health care problem in developing countries and is the second commonest neurological disorder after headache in India. ^[1] The mainstay of treatment of epilepsy is AEDs and that for varying duration of few months to lifelong. Approximately 65% of patients with new-onset epilepsy will eventually become seizure free. ^[6]

Aims: The aim of this study was to evaluate the outcome of medical treatment modifications in patients with drug-resistant epilepsy.

Results: 21 patients were enrolled into the study after obtaining the written informed consent. Different AEDs were added to these 21 patients in addition to their previous regimen. Proportion of patients who achieved seizure remission were 8 (38%) out of total 21 patients. There is significant reduction in seizure frequency after modifying the treatment regimen.

Conclusion: Our study findings provide evidence that seizure remission can occur in a proportion of adult patients with chronic and intractable epilepsies. Newer AEDs like TPM, LTG, LEV could be good alternatives as add-on drugs in patients with DRE.

Keywords: Epilepsy, Antiepileptic Drugs, Drug resistant epilepsy, Resistance

Introduction

Epilepsy is a major health care problem in developing countries and is the second commonest neurological disorder after headache in India. ^[1] It is a common neurologic disorder with potentially devastating consequences on individual lives, inflicting unemployment, social isolation, comorbidities, and relentless stigmatization.

The mainstay of treatment of epilepsy is AEDs and that for varying duration of few months to lifelong. Approximately 65% of patients with new-onset epilepsy will eventually become seizure free. ^[6]

Despite optimal therapy with AEDs, approximately one-third of epileptic patients do not achieve remission of seizures and this group of patient is considered to have intractable, refractory or AED-resistant epilepsy (RE). ^[9] Nevertheless, RE could be defined "as the persistence of correctly diagnosed unprovoked epileptic seizures that recur so frequently that they interfere with patients' daily lives and cause personal dissatisfaction." Thus, a patient may be considered as exhibiting RE after receiving treatment with 2 first-choice AEDs or a combination of 2 first-line AEDs appropriate to the type of seizures and

epileptic syndrome of the patient at the maximum tolerated doses and with good compliance.

Drug-Resistant Epilepsy (DRE)

It is defined as the failure of adequate trials of two tolerated, appropriately chosen and administered antiepileptic drugs (whether as monotherapy or in combination) to achieve sustained seizure freedom. “Intractable” and “refractory” would imply that there is no chance of remission at all, which is never the case. ^[11] Approximately 20 to 40 percent of patients with epilepsy are likely to have refractory epilepsy. ^[12]

Factors that characterize Refractory Epilepsy ^[15]

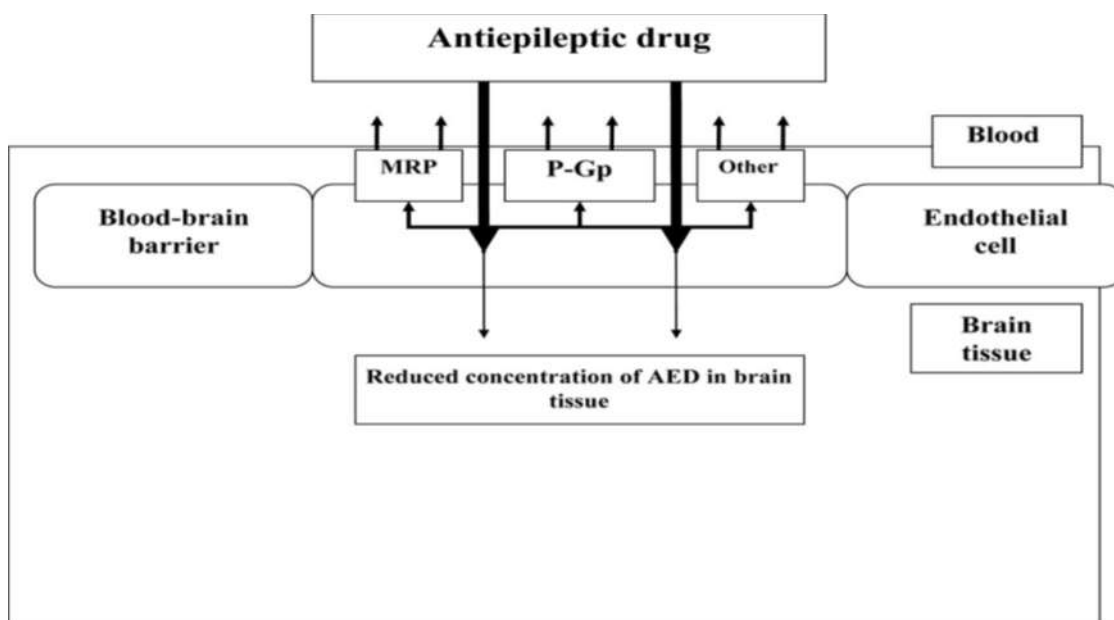
1. Intractable seizures

2. Excessive drug burden
3. Neurobiochemical plasticity changes
4. Cognitive deterioration
5. Psychosocial dysfunction
6. Dependent behaviour
7. Restricted lifestyle
8. Unsatisfactory quality of life

Mechanism of Pharmacoresistance

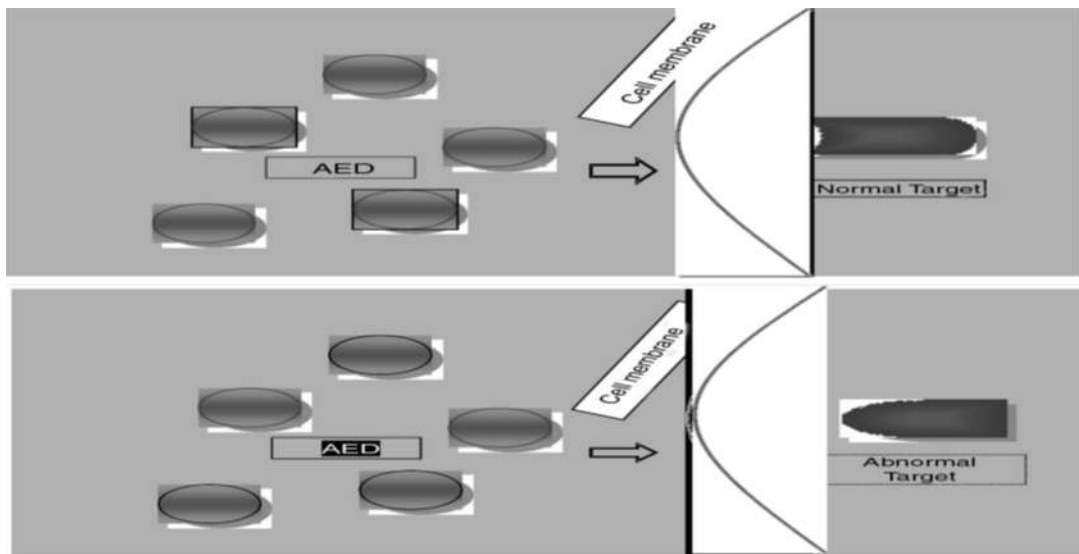
Two main hypotheses have been proposed for DRE:

Pharmacokinetic or “Transporter” hypothesis:



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Pharmacodynamic or “Target hypothesis”:



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The goals of treatment are complete freedom from seizures with no (or acceptable adverse effects) and the maintenance of a normal lifestyle. AEDs currently licensed for common use as monotherapy include carbamazepine, phenytoin, phenobarbital, ethosuximide, sodium valproate, lamotrigine, topiramate, oxcarbazepine and levetiracetam.^[22] most frequent type of death in patients with pharmacoresistant epilepsy.

Interventions to improve health-related quality of life (HRQOL) in patients with medication-resistant epilepsy should focus on treating mood disturbances and minimizing medication adverse effect.^[33]

This study has been planned to evaluate the effects of modification of AED treatment to the previous regimen in patients with DRE which ultimately may improve the seizure control.

Material And Methods

This prospective, observational study was conducted over a period of 15 months in the outpatient department of neurology and epilepsy clinic at a tertiary health care centre in Punjab (India) after approval from Institutional Thesis Ethics Committee.

Screening was done for the two months, of all those patients whose previous records were available at our epilepsy centre. . Based upon their various parameters like age at onset, duration of epilepsy,

previous no. of AEDs failed i.e. patients who fulfilled all the inclusion criteria and none of the exclusion criteria were enrolled Lastly, we included those patients who gave consent for the same and were followed-up for duration of one year after modification of AED treatment

Inclusion Criteria:

1. Age: > 16 years
2. Gender: either
3. On AED treatment > 2 years
4. Seizure frequency > 1 per month for the 3 months prior to the index date (enrollment date)
5. Failed 2 or more AEDs at maximum tolerable dose prior to the index date (enrollment date)

Exclusion Criteria:

1. Non-consenting patients
2. Non-epileptic seizures

The record of 583 patients were evaluated who were attending the epilepsy clinic for the last few years. The eligible patients among them were selected (N=213) for the study and were then screened for the 2 months. These patients were then informed about the study. Out of these, only 51 patients consented on phone to participate, but only 22 patients signed the consent form for the study. Among these 22 patients, one was excluded from the study as he was fit for epilepsy surgery after presurgical evaluation. Out of 583 patients, finally 21 patients were enrolled into the study after obtaining the written informed consent . Different AEDs that were added to these 21 patients

in addition to their previous regimen and their outcome is shown (Table 1).

Appropriate AEDs were prescribed to the patients so that optimal seizure control was achieved with modified regimen with minimal adverse effects. The follow-up was carried out every three monthly and final evaluation was done at the end of one year.

Outcome Parameters:

Observations And Results

Proportion of patients who have achieved seizure remission for atleast 6 months from the time period between the date of enrollment to the date of exit / last follow up in the study, were noted. Patients were then entered into Kaplan-Meier type survival analysis and were allowed to exit the study once they have achieved a continuous period of 6 months remission or complete the one year study period.

Table 1 Medical Treatment Modifications

Drug added to Rx	Patients (n)	n, Patients with Seizure remission	n, Percent reduction in Seizure frequency
TPM	4	2	2, (42.6%, 53.3%)
LTG	4	2	2, (53%, 33.3%)
OxCBZ	4	0	4, (57.2%, 54.8%, 36%, 13.3%)
LEV	3	1	2, (45.8%, 25%)
LCM	1	0	1, (25%)
LEV & OxCBZ	2	1	1, (16.6%)
LEV & TPM	1	1	0
LEV & CBZ	1	1	0
VPA & CBZ	1	0	1, (41.6%)

Table 2 Demographics And Clinical Characteristics Of Patients In Drug-Resistant Epilepsy

Sex	
Male	15 (71.4%)
Female	6 (28.6%)
Mean age (years)	27.1 ± 9.35
Mean age at onset (years)	12.5 ± 7.81
Diagnosis	
Temporal lobe epilepsy	10 (47.6%)
Frontal lobe epilepsy	7 (33.3%)
Mesial temporal lobe epilepsy	3 (14.3%)
Frontotemporal lobe epilepsy	1 (4.8%)

Mean duration of epilepsy	14.7± 5.54
Follow-up (years)	1
Mean time to first seizure remission (months)	2.8 ± 3.80

Table 3 Previous And After Seizure Frequency

Seizure frequency	Mean±SD	Range	t-value	Pearson Correlation	p-value
Previous	6.0 ± 2.70	2-12	6.797	.709	0.000
After modifying regimen	3.1 ± 1.51	0.8-5.4			

Table 4 Percent Reduction In Seizure Frequency

Percent reduction in seizure frequency	Number of patients
< 50 % reduction	11
50 % reduction	1
> 50 % reduction	9

Table 5 Previous Number Of Aeds And Percent Reduction In Seizure Frequency

Number of drugs previously taken	n	Less than 50% reduction in seizures, n (%)	50-99% reduction in seizures, n (%)	Seizure free, n (%)
<5	10	4 (40%)	2 (20%)	4(40%)
≥5	11	2 (18.2%)	5 (45.5%)	4 (36.3%)

Table 6 Duration Of Epilepsy And Percent Reduction In Seizure Frequency

Duration of epilepsy (years)	n	Less than 50% reduction in seizures, n (%)	50-99% reduction in seizures, n (%)	Seizure free, n (%)
5-10	7	4 (57.1%)	1 (14.2%)	2 (28.6%)
11-15	4	3 (75%)	0 (0%)	1 (25 %)
16-20	7	2 (28.6%)	2 (28.6%)	3 (42.8 %)
>20	3	0 (0%)	1 (33.3%)	2 (66.7%)

Discussion

Drug-resistant epilepsy (DRE) also known as difficult-to-control or intractable or

pharmacoresistant or refractory epilepsy. Studies have shown that AED treatment can induce long-term seizure remission in up to 70% of epileptic patients.

The remaining 30% of epileptic patients have DRE and continue to experience seizures despite appropriate AED treatment.^[101]

We found that most of the patients in this study belong to the age group 16-25 years. Mean age of the patients was 27.1 ± 9.35 years and the median age of patients was 28 years with IQR of 18-33 years.

Mean seizure frequency before modifying the AED treatment was 6.0 ± 2.7 and after, seizure frequency was significantly reduced to 3.1 ± 1.51 ($p=0.000$) (Table 7).

Percent reduction in seizure frequency in all patients according to number of previous AEDs taken (Table 15) and duration of epilepsy (Table 16) is shown. This showed there is significant correlation exists between percent reduction in seizure frequency and duration of epilepsy (Table 18).

Out of 21 patients, 8 patients (38%) became seizure free with a mean time to first seizure remission of 2.8 ± 3.80 months.

In our study, duration of epilepsy was statistically significantly (p -value=0.029) correlated ($r=-0.477$) with seizure frequency after modifying regimen. Seizure frequency was significantly decreased although no significant association with seizure remission. We found that the longer the duration of epilepsy, smaller the rate of greater than 50% reduction in seizure frequency.

The percentage of patients rendered seizure free by the new drug was greater in those who had been previously treated with less than 5 drugs (40%) compared with (36%) of those who had previously taken 5 or more drugs (Table 16).

In this study, 39% of patients had a seizure reduction of $\geq 50\%$ and 13% became seizure-free for at least 6 months. In our study, 4 patients were given lamotrigine in addition to valproate, out of which 2 patients (50%) became seizure free, 1 patient had 53% reduction in seizure frequency and 1 patient had 33.3% reduction in seizure frequency.

This can be emphasized from our study, that an important percentage of patients in this refractory population could have a significant improvement in their seizure control even if they do not achieve sustained remission.

Summary And Conclusion

The following results were observed:

1. Proportion of patients who achieved seizure remission were 8 (38%) out of total 21 patients.
2. There is significant reduction in seizure frequency after modifying the treatment regimen.
3. Number of patients who achieved seizure remission on adding drugs to their previous regimen with TPM (2), LTG (2), LEV (1), combination of LEV & OxCBZ (1), combination of LEV & TPM (1), combination of LEV & CBZ (1).
4. None of the variables like age, age at onset, duration of epilepsy, previous seizure frequency, no. of previous AEDs taken shown significant association with seizure remission.
5. The following conclusions can be drawn from this study are:
6. Our study findings provide evidence that seizure remission can occur in a proportion of adult patients with chronic and intractable epilepsies.
7. Newer AEDs like TPM, LTG, LEV could be good alternatives as add-on drugs in patients with DRE.
8. One main conclusion from this study that no matter how many AEDs have been tried in the past, there is always hope that a patient with DRE will have a significant reduction in seizure frequency or can even achieve seizure remission.

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