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# Experience with new antiepileptic drugs among Indians with refractory epilepsy

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### *Abstract*

*Objectives:* We assessed the comparative efficacy and tolerability of topiramate (TPM), lamotrigine (LTG), gabapentin (GBP) and clobazam (CLB) with an aim to formulate clinical guidelines while initiating treatment with new anti-epileptic drugs (AEDs). *Methods:* A prospective open label, non-randomized, add-on study was conducted on 203 Indian patients with seizures refractory to conventional AEDs (age 1-63yrs, mean age 19.4±13.4 yrs) who were started on any of the four new AEDs, as and when the AEDs were available, either singly or in combination. Patients were prospectively followed up for a minimum period of four months and the 50% seizure reduction, seizure freedom, adverse events and cost of daily therapy were assessed. *Results:* At the end of four months, 166 patients had completed follow up. Baseline seizure frequencies were significantly different across the groups ($p<0.01$). The proportion of patients with >50% seizure reduction, seizure freedom, adverse events and the increase in cost over the baseline respectively were: TPM (63 patients) (51%, 13%, 52%, 4 times), LTG (62 patients) (73%, 27%, 34%, 3 times), CLB (16 patients) (69%, 56%, 56%, 2 times) and patients on two of these new AEDs (25 patients) (52%, 16%, 40%, 4 times). The seizure change across all the groups was similar.
*In conclusions:* The three new AEDs studied (TPM, LTG, CLB) resulted in similar seizure control when used as add on therapy. Based on cost, we recommend addition of the new AEDs sequentially: CLB, LTG and TPM in that order and then try a combination of two new AEDs.

## INTRODUCTION

Epilepsy affects 2-3% of the population.[1] The prevalence of epilepsy in India ranges from 1.71 to 11.9 (mean 5.35) per 1000 population.[2] Approximately 20% of patients have refractory epilepsy despite optimal anti-epileptic drugs (AEDs).[3] In randomized controlled trials (RCTs) many new AEDs are reported to be more effective than placebo in the treatment of refractory seizures in adults and children.[4] A meta-analysis of RCTs involving the new AEDs reported similar efficacy or tolerability of topiramate (TPM), gabapentin (GBP), lamotrigine (LTG), tiagabine, vigabatrin and zonisamide.[5] These studies have been mainly conducted in the developed countries. There is limited data on the usefulness of new AEDs among Asians. The new AEDs being more expensive than the conventional AEDs, their affordability is a major problem in developing countries. We report our experience on the comparative efficacy, tolerability and cost of TPM, LTG, GBP and clobazam (CLB) among patients with refractory epilepsy treated at a tertiary care hospital in northern India.

## METHODS

All cases of refractory epilepsy (age > 1 year) attending the Neurology outpatient department of All India Institute of Medical Sciences, New Delhi, India who were started on TPM, LTG, CLB or GBP were included in the study and prospectively followed up on a bimonthly basis for 6 months. Refractory epilepsy was defined as seizures frequent or severe enough to interfere with the quality of life or if the patient developed intolerable side effects when on maximally tolerated doses of one or more AEDs without seizure control.[6] Patients with progressive neurological disorders and pseudoseizures were excluded from the study. Video EEG recording was obtained for the diagnosis in cases suspected to have pseudoseizures.

### *Patient selection and seizure classification*

This was an open label, non-randomized study. All patients studied were interviewed in detail and examined by one author (SJ). Patient demographic data, age of onset of seizures, type of seizure, epileptic syndrome, history of status

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epilepticus, febrile convulsions, family history of epilepsy and other risk factors for epilepsy were recorded in a pre-designed proforma by one author (PRK). EEGs were done in all patients. CT/MRI brain scans were done if indicated. Seizures were classified according to the ILAE classification of epileptic seizures[7] and epilepsies were classified according to the ILAE classification of epilepsy and epileptic syndromes[8] by one author (SJ).

*Initiation of new AED therapy*

All patients received oral therapy. Baseline monthly seizure frequency during previous 6 months and body weight was recorded. TPM was started at a dose of 25mg daily, and increased at fortnightly intervals by 25-50mg up to a maximum of 10mg/kg/day. Children were started on TPM at a dose of 0.5mg/kg/day and titrated similarly. LTG was started as 25mg on alternate days for 2 weeks then increased to 25mg daily in patients on Valproate increasing up to 5mg/kg/day. In patients not on valproate, 25-50mg/day of LTG was started and increased every two weeks. GBP was started in the dose of 900-2400 mg/day.[9] CLB was introduced as 5-10mg/day increasing over 2-3 weeks up to 0.5mg/kg/day. All new AEDs were tried to the minimum effective or maximally tolerated dose. Although the groups were not strictly comparable in terms of the number of AEDs used, the patients could be treated with any combinations of conventional (valproate, carbamazepine, phenytoin, phenobarbitone, clonazepam and new AEDs (TPM, LTG, CLB or GBP) before inclusion in the study. In case of early intolerance to any of the new AEDs, the titration phase was extended suitably to the patients' benefit or the new AED was withdrawn if considered necessary.

*Follow-up and assessment of efficacy of new AEDs*

Patients were prospectively followed up at bimonthly intervals. The monthly seizure frequency and adverse events for a period of 6 months were recorded. Patients were compared at a minimum follow up of 4 months and were divided into four groups based on the new AED they received at entry (TPM, LTG, CLB alone and patients receiving two new AED). Only one patient receiving GBP alone and was excluded from analysis. The baseline seizure frequency among all the groups was taken as the seizure frequency before addition of the first new AED. Seizure control was calculated as >50% reduction and <50% reduction in seizure frequency from the baseline. The seizure change over 4 months (absolute seizure reduction) was calculated as the difference in seizure frequency between baseline and follow up at 4 months.

Cost of therapy was calculated in Indian Rupees (1US$=47 INR) based on the price of the lowest available dose unit of one leading brand. The dose units taken for calculation were: 100mg for Phenytoin, 200mg for Cabamazepine and Valproate, 30 mg for Phenobarbitone, 0.5mg for Clonazepam, 25mg for TPM and LTG, 5mg for CLB and 300mg for GBP. These units were used to calculate the cost of the daily total dose of one or more conventional or new AEDs. The mean daily cost of conventional and new AEDs was also calculated for each group for comparison.

*Statistical analysis*

Data was entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 10 statistical software for Windows and Systat 7 for Windows. Subgroup analysis was done in each of the four groups between those with >50% seizure reduction and <50% seizure reduction. The four groups were then compared against each other on all variables. The categorical variables were compared using Pearson's chi square or Fisher's exact test and continuous variables were compared using the t test or Wilcoxon rank sum test. Kruskall Wallis test was used to compare the seizure frequency across all the 4 groups. Logistic regression was done to further analyze the four groups with the dichotomous variables of 50% seizure reduction and side effects. Statistical significance was considered when $p \leq 0.05$.

## RESULTS

A total of 203 patients, 138 males (68%) and 65 females (32%) with mean age 19.5±13.5years, mean age at seizure onset 9.0±10.0 years and mean duration of seizures 10.4±8.1 years were included into the study. Partial seizures were seen in 150 patients (74%), generalized seizures in 27 (13%) and multiple seizure types in 26 (13%). Eighteen patients (9%) had past history of status epilepticus. Family history of seizures was seen in 43 patients (21%). EEGs were normal in 45 (22%), showed focal discharges in 103 (52%), generalized discharges in 32 (16%) and multifocal discharges in 23 (11%) patients. CT scan of the head was normal in 48 patients (24%) and abnormal in 57 patients (28%). MRI brain was normal in 50 (25%), abnormal in 105 (52%) that

included mesial temporal sclerosis in 22 (10%).

Three patients (1.5%) were not on any conventional AEDs, 116 (57%) were on single, 81 (40%) on two and 3 patients (1.5%) were on 3 conventional AEDs. Of these, 105 patients were on VPA, 136 on CBZ, 26 on PHT, 9 on Phenobarbitone and 10 on Clonazepam either alone or in combinations. One new AED was being taken by 173 patients (86%) and two by 30 patients (14%). Of these, 72 patients were on TPM, 79 on LTG, 21 on CLB, 1 on Gabapentin and 30 were on 2 new AEDs. Adverse events occurred in 78 patients (38%). The patient on Gabapentin was excluded for subgroup analysis.

On the whole 64% of patients (101 of 166 patients followed up at 4 months) were documented to have >50% seizure reduction and seizure freedom was achieved in 38 patients (23%).

*Topiramate group*

The demographic and clinical details of 72 patients on TPM are summarized in Tables 1 & 2. Sixty-three patients completed 4 months follow up and were analyzed. Thirty-one patients (49%) had a <50% seizure reduction, 32 patients (51%) had >50% seizure reduction and 8 patients (13%) became seizure free. The age group, age of onset and duration of seizures, type of seizure, epileptic syndrome, family history of epilepsy, EEG, MRI and conventional AEDs data were comparable in both groups (<50% and >50% seizure reduction). Mean dose of TPM was 116.1±64.1mg/day in those with <50% seizure reduction and 149.2±95.1mg/day in the group with >50% seizure reduction. Adverse events were seen in 17 patients (55%) with <50% seizure reduction and 16 (50%) patients with >50% seizure reduction. Cognitive and behavioral changes, worsening of seizures and weight loss were the prominent adverse effects. Twelve patients (17%) discontinued TPM, 11 due to seizure worsening and 1 due to adverse events alone.

*Lamotrigine group*

Sixty-two of 79 patients on LTG completed 4 months follow-up (Tables 1& 2), 17 (27%) had <50% seizure reduction, 45 patients (73%) had >50% seizure reduction and 17 (27%) achieved seizure freedom. There were two significant differences between patients with <50% and >50% seizure reduction. Valproate dose was 590±255.9mg/day in those with <50% seizure reduction and 1152±422.4mg/day in the group with >50% seizure reduction (p=0.007) while mean duration of seizures in those with <50% seizure reduction was 7.8±6.9 years and in those with >50% seizure reduction it was 13.3±9.0 years (p=0.037). No statistically significant differences were observed between the groups with <50% and >50% seizure reduction with regards to other variables. Mean dose of LTG in the group with <50% seizure reduction was 126.5±84.5mg/day and in those with >50% seizure reduction it was 111.7±72.6mg/day. Adverse events were seen in 4 patients (24%) with <50% seizure reduction and 18 patients (40%) with >50% seizure reduction. Drowsiness and cognitive changes were the main adverse events seen. No patient had seizure worsening on LTG alone.

*Clobazam group*

Sixteen of 21 patients on CLB completed 4 months follow-up (Tables 1 & 2). Five patients (31%) had <50% seizure reduction, 11 patients (69%) had >50% seizure reduction and 9 patients (56%) became seizure free. No significant differences were observed between the groups with <50% and >50% seizure reduction regarding patient characteristics. Mean dose of CLB was 19±12.5mg in those with <50% seizure reduction and 15±9.49mg/day in patients with >50% seizure reduction. Adverse events occurred in all patients (5, 100%) with <50% seizure reduction and 5 patients (46%) with >50% seizure reduction. Drowsiness was the main adverse effect. One patient had seizure worsening necessitating drug discontinuation.

*Group on 2 new AEDs*

Of the thirty patients on two new AEDs (Tables 1& 2) 12 were on a combination of TPM+LTG; 9 on TPM+CLB; 2 on TPM+GBP and 7 on LTG+CLB. At the end of 4 months, 25 patients were available for analysis: 12 patients (48%) had <50% seizure reduction, 13 patients (52%) had >50% seizure reduction and 4 patients (16%) became seizure free. A family history of epilepsy was seen in 4 patients (33.3%) who had <50% seizure reduction compared to none in those with >50% reduction (p=0.023). Remaining variables were comparable between the two groups. Subgroup analysis did not show any particular combination of new AEDs to be superior or had greater incidence of adverse effects probably as the number of patients in this group was very small. Adverse events were seen in 6 (50%)

**TABLE 1: Demographics and clinical features of patients in the four groups**

| | **Topiramate** (N=72) | **Lamotrigine** (N=79) | **Clobazam** (N=21) | **Two new AEDs*** (N=30) |
|---|---|---|---|---|
| | Mean ± SD | Mean ± SD | Mean ± SD | Mean ± SD |
| Age at presentation in years | 16.9±13.6 | 20.9±12.5 | 21.1±13.3 | 19.8±15.0 |
| Seizure duration in years | 9.1±7.1 | 11.3±8.8 | 9.4±6.7 | 11.3±9.1 |
| Male, n (%) | 46 (64) | 56 (71) | 15 (71) | 21 (70) |
| Female, n (%) | 26 (36) | 23 (29) | 6 (29) | 9 (30) |
| Age of onset in years | 7.9±10.2 | 9.5±8.9 | 11.8±13.5 | 7.8±9.3 |
| Age group, n (%) | | | | |
| 0-10 years | 24 (33) | 16 (20) | 5 (24) | 9 (30) |
| 10-20 years | 30 (41) | 30 (38) | 7 (33) | 10 (33) |
| 20-30 years | 9 (13) | 16 (20) | 6 (29) | 5 (17) |
| >30 years | 9 (13) | 17 (22) | 3 (14) | 6 (20) |
| Age of seizure onset, n (%) | | | | |
| 0-10 years | 55 (76) | 51 (65) | 13 (62) | 21 (70) |
| 10-20 years | 9 (12) | 17 (21) | 3 (14) | 6 (20) |
| 20-30 years | 4 (6) | 8 (10) | 4 (19) | 2 (7) |
| >30yrs | 4 (6) | 3 (4) | 1 (5) | 1 (3) |
| Type of seizure, n (%) | | | | |
| Partial/PSGTCS† | 40 (56) | 68 (86) | 17 (81) | 24 (80) |
| Primary generalized | 16 (22) | 7 (9) | 3 (14) | 1 (3) |
| Multiple seizure types | 16 (22) | 4 (5) | 1 (5) | 5 (17) |
| History of status epilepticus, n (%) | 8 (11) | 5 (6) | 1 (5) | 4 (13) |
| Family history of epilepsy, n (%) | 17 (24) | 18 (23) | 2 (10) | 6 (20) |
| No of conventional AEDs, n (%) | | | | |
| None | 1 (1) | 0 | 0 | 2 (7) |
| 1 drug | 39 (54) | 49 (62) | 12 (57) | 16 (53) |
| 2 drugs | 30 (42) | 29 (37) | 9 (43) | 12 (40) |
| 3 drugs | 2(3) | 1(1) | - | - |
| No of patients with past poor response to other new AEDs, n (%) | | | | |
| 1 new AED | 29 (71) | 6 (8) | 4 (19) | 10 (33) |
| 2 new AEDs | 11 (27) | - | - | 1 (3) |
| 3 new AEDs | 1 (2) | - | - | - |

*AEDs- Anti-epileptic drugs
†PSGTCS- partial with secondary generalized seizure

**TABLE 2: AED therapy, seizure frequency and cost details of patients in the four groups**

| | **Topiramate** (N=72) | | **Lamotrigine** (N=79) | | **Clobazam** (N=21) | | **Two new AEDs** (N=30) | |
|---|---|---|---|---|---|---|---|---|
| | n | mean±SD | n | mean±SD | n | mean±SD | n | mean±SD |
| Conventional AEDs | | | | | | | | |
| Valproate | 43 | 783.7±438.6* | 38 | 978.9±444.1* | 9 | 1044.4±339.5* | 14 | 821.4±353.4* |
| Carbamazepine | 45 | 693.3±314.4* | 49 | 702±274.9* | 18 | 750±301.5* | 23 | 773.9±327.8* |
| Phenytoin | 4 | 250±57.7* | 16 | 257.8±99* | 4 | 225±50* | 2 | 300* |
| Phenobarbitone | 2 | 45±21.2* | 6 | 75±25.1* | - | - | 1 | 60* |
| Clonazepam | 7 | 1.86±1.07* | 3 | 0.83±0.29* | - | - | - | - |
| New AEDs | | | | | | | | |
| Topiramate | 72 | 122.6±82.2* | - | - | - | - | 23 | 97.8±69.4* |
| Lamotrigine | - | - | 79 | 103.8±75.2* | - | - | 19 | 111.8±76.5* |
| Clobazam | - | - | - | - | 21 | 13.9±9.96* | 16 | 12.0±5.9* |
| Gabapentin | - | - | - | - | - | - | 2 | 900±424.3* |
| Baseline seizure Frequency/month | 72 | 139.3±434.9 | 79 | 49.3±205.1 | 21 | 12.48±32.7 | 30 | 32.6±48.8 |
| Seizure frequency/ month at 4 months | 63 | 115.7±436.7 | 63 | 4.25±9.69 | 21 | 1.36±2.71 | 25 | 26.8±42.8 |
| Baseline seizure frequency (median) | | 9.5 | | 3 | | 2 | | 9 |
| Seizure frequency at 4 months (median) | | 5 | | 2 | | 0 | | 5 |
| Cost of conventional AED per day in INR[#] | | 8.6±5.4 | | 8.5±5.0 | | 9.7±6.7 | | 8.6±4.7 |
| Cost of new AED per day in INR[#] | | 20.7±14.1 | | 12.6±9.5 | | 7.0±5.0 | | 23.3±16.3 |
| Total cost of AEDs per day in INR[#] | | 29.5±15.3 | | 21±11.1 | | 16.7±11.2 | | 31.6±15.3 |

* Daily dose of the drug (mg/day)
[#]INR- Indian Rupees, 1 US$=47 INR.

patients with <50% seizure reduction and 4 (31%) patients with >50% seizure reduction. Main adverse events were seizure worsening; 4 patients (16%) discontinued TPM and 1 patient discontinued LTG due to seizure worsening. When the seizure control before the addition of the second new AED was considered, it was found that 32% (8 of 25 patients) had achieved a >50% reduction in seizure frequency while on the first new AED which increased to 52% (13 of 25 patients) after addition of the second new AED at the end of 4 months (p=0.15). Thus only 20% of patients had actually benefited with the addition of the second new AED.

*Inter-group comparisons*

The two main groups of patients on TPM (n=63) and LTG (n=62) were compared. More patients with primary generalized seizures (22% in TPM group versus 9% in LTG group, p=0.06) and multiple seizure types (22% in TPM group vs 4% in LTG group, p=0.001) were on TPM. Baseline seizure frequency (p=0.002) and seizure frequency at end of study (p=0.000) were significantly higher

among patients on TPM (Table 2, Mann-Whitney test). More patients in TPM group had side effects compared to those on LTG (52% versus 34%, p=0.031). Patients on LTG had better >50% seizure reduction rate compared to TPM (73% versus 51%, p=0.012) and also better seizure freedom rates (27% of patients on LTG compared to 13% patients on TPM, p=0.044). However, the seizure change (difference in seizure frequency at 4 months from the baseline) was not significantly different between the two groups (Mann-Whitney test, p=0.92). Thus, the apparently better effect seen may be related to the significantly lower baseline seizure frequency among patients on LTG.

In the inter-group comparison, patient characteristics were mostly similar. The significant differences among 4 groups being more patients with primary generalized and multiple seizure types in the TPM group than in the others while partial seizures were more common in other groups (Table 1, p=0.001). In the LTG group compared to the TPM group, there were more cases with localization related symptomatic epilepsies (79% versus 63%, p=0.030). Also more patients in TPM group had tried other new AEDs in the past before being started on TPM (41 patients in TPM group, 6 in LTG group, 4 in CLB group and 11 in the two new AED group, p=0.05). Baseline seizure frequency and seizure frequency at end of 4 months were significantly different in the 4 groups (both p<0.001). However the seizure change among the groups at 4 months (obtained by subtracting the frequency at 4 months from the baseline seizure frequency) was not significant among the four groups (Kruskal Wallis test, p=0.996). Thus, there seems to be no overall difference in efficacy among the four groups regarding seizure change at 4 months ( >50% seizure reduction) and adverse events. Seizure freedom was significant across the groups (p=0.002) (Table 4).

Since TPM was the latest entrant into the Indian market, many patients had been started on TPM after trials with other new AEDs had been unsuccessful. We compared those in whom TPM was the first add-on with those in whom it was the second or third add-on as regards 50% seizure reduction. Ten of 22 (45%) patients with TPM as first add-on had >50% seizure reduction compared to 22 of 41(54%) in whom TPM was the second or third add-on, the difference was statistically not significant. Hence, efficacy wise, it does not seem to matter if TPM has been tried as the first or subsequent add-on.

Logistic regression was applied to further study the effect of variables on 50% seizure reduction and side effects. No factors influenced the 50% seizure reduction. Side effects were influenced by two factors, the presence of a past history of status epilepticus (risk ratio 1.85) and if one or more new AED had been tried in the past excluding the present one (risk ratio 2.34). Logistic regression was not done for those with seizure freedom due to small numbers.

*Cost analysis*

The cost of baseline conventional AEDs was similar across all groups (Table 2). There was significant increase in cost due to addition of TPM compared to LTG (p<0.001) and CLB (p<0.001) but not with the group on 2 new AEDs. Cost accrued by the group on 2 new AEDs was significantly higher compared to LTG (p=0.014) and CLB (p=0.003). There was no significant difference between the cost incurred by those with <50% and >50% seizure reductions among patients on each of the new AEDs. The addition of 2 new AEDs raised the daily cost of therapy marginally when compared to the group on only TPM. Thus, by adding TPM or a combination of 2 new AEDs to existing conventional AEDs, the daily cost of therapy was increased almost 4 times the baseline cost incurred on only conventional AEDs; adding LTG raised costs 3 times and adding CLB doubled the daily cost of AED therapy.

## DISCUSSION

Many new AEDs have been introduced in recent years to improve seizure control among patients with seizures refractory to conventional AEDs. RCTs have shown efficacy of these drugs in patients with refractory epilepsy compared to placebo.[4,5] There has been an effort to compare these drugs in a meta-analysis[5], but there is no single study comparing the new AEDs with each other. Our study is perhaps the first one of its kind comparing the commonly available new AEDs against each other.

Randomized controlled trials on TPM have shown >50% seizure reduction in 35-52% of patients with refractory partial epilepsy.[4] Adverse events have been found in 30-73% of patients.[5, 10,11] A Korean RCT[12] demonstrated 51% of patients was able to achieve >50% seizure reduction. An open label all-Asia study[13] showed a >50% seizure reduction in 56%. TPM has been found to be

effective in children[14,15], primary and secondary generalized seizures.[4,16] In our study, >50% seizure reduction occurred in 51%, seizure freedom was achieved in 13% of patients and adverse events were observed in 52%. These results are comparable to other studies. Variable degree of seizure worsening was noted in 11 patients (16%) necessitating withdrawal of TPM. Others have found seizure worsening to occur in 6-8% of patients only.[15,17] The higher incidence of seizure worsening due to TPM appears to be peculiar to Indians. It is a common experience that adverse drug reactions are related to the dose of AEDs used. Our observation of a greater incidence of adverse effects among those who received a lower mean dose of TPM was mainly due to the fact that many patients among this group had stopped TPM due to seizure worsening at a very low dose. The high cost of new AEDs like TPM in developing countries like India restricts the

**TABLE 3. Adverse events among patients in the four groups**

| Adverse events | **Topiramate** N=63 | **Lamotrigine** N=62 | **Clobazam** N=16 | **Two new AEDs** N=25 |
|---|---|---|---|---|
| Drowsiness | 3 | 7 | 5 | 2 |
| Decreased appetite | 6 | 4 | 1 | 1 |
| Nausea | 2 | 0 | 1 | 0 |
| Behavioral abnormality | 1 | 0 | 0 | 0 |
| Cognitive | 3 | 5 | 2 | 1 |
| Weight loss | 7 | 0 | 0 | 0 |
| Irritability | 4 | 2 | 1 | 1 |
| Skin rash | 1 | 0 | 0 | 0 |
| Blurring of vision | 0 | 2 | 1 | 0 |
| Giddiness | 1 | 3 | 0 | 1 |
| Seizure worsening | 11 | 0 | 1 | 5 |
| Increased aggressiveness | 3 | 0 | 0 | 1 |
| Headache | 0 | 1 | 1 | 1 |
| Ataxia | 1 | 1 | 0 | 0 |
| Weight gain | 2 | 1 | 0 | 1 |
| Fatigue | 2 | 1 | 0 | 0 |
| Skin pigmentation | 1 | 0 | 1 | 0 |
| Tremors | 0 | 5 | 0 | 1 |
| Total patients with adverse events, n (%)* | 33 (52) | 21 (34) | 9 (56) | 10 (40) |

* Each patient can have more than 1 adverse event

**TABLE 4. Comparison of seizure reduction and adverse events in the four groups**

| | **Topiramate** N=63 | **Lamotrigine** N=62 | **Clobazam** N=16 | **Two new AEDs** N=25 | p value |
|---|---|---|---|---|---|
| >50% Seizure reduction at 4 months | 51% | 73% | 69% | 52% | 0.059 |
| Seizure freedom at 4 months | 13% | 27% | 56% | 16% | 0.002 |
| Adverse events | 52% | 34% | 56% | 40% | 0.14 |

dose in which these drugs can be used and may explain the lower occurrence of cognitive impairment in the Indian population.

LTG has been found to reduce seizures by >50% in 20-50% of patients[5] in RCTs. Jawad *et al*[18] have found 50% seizure reduction in 66% of patients. Seizure freedom was achieved by 11% of patients.[4] In our study, 73% patients had a >50% seizure reduction and 27% became seizure free. The beneficial effect of LTG in our study is better than reported in other studies. This may be due to differences in efficacy and tolerability of LTG among the Indians with refractory epilepsy and needs further study. Adverse events were found in 40% of patients in pooled RCTs.[5] In our study, adverse events occurred in 36% patients, which is similar. The lower dose of LTG used among those with >50% seizure reduction and higher dose used among those with <50% seizure reduction is probably due to the fact that the dose of LTG was not increased among those who had good response while a higher dose was attempted among those with a poor response. A higher dose of Valproate among better responders could have also contributed to the antiepileptic effect. The better response to LTG among those with epilepsy for a longer duration and higher incidence of adverse effects among those on a lower dose of LTG are intriguing observations that need to be verified in studies with much larger number of patients.

In our study, CLB produced >50% seizure reduction in 11 (69%), 9 patients (56%) became seizure free and 9 patients (56%) had adverse events. Koeppen *et al*[19] found that 15% became seizure free. In a study by Schmidt et al[20], 40% had >75% seizure reduction, 20% became seizure free and adverse events occurred in 40% of patients. Allen et al[21] found that >50% seizure reduction occurred in 59% of patients. A meta-analysis of studies on CLB found that >50% seizure reduction occurred in 65% of patients and 38% had adverse events.[22] In our study, the >50% seizure reduction has been similar but both seizure freedom and side effects have occurred in a higher percentage of patients. This again could reflect some peculiarity in metabolism of CLB among Indians pointing to the problems associated with extrapolating data from studies conducted in different populations.

In the group on 2 new AEDs, 13 (52%) had a >50% seizure reduction; 4 (16%) became seizure free and 10 (40%) experienced adverse events. Two patients in this group were on GBP. RCTs on GBP have found that up to 35% of patients achieve a >50% seizure reduction.[4] A previous study from our center had reported a >50% seizure reduction in 50% of patients and 46% had adverse events.[23] Adding an additional new AED to the existing one produced a further reduction in seizure frequency in 20% patients without any significant increase in adverse events. Hence such an option may be worthwhile in some patients. There are no comparative data available of similar studies in patients on more than one new AED.

Comparing all the 4 groups, the seizure change (absolute seizure reduction), 50% seizure reduction and adverse events in the 4 groups were statistically not significantly different. A systematic review of the new AEDs[5] found that across many RCTs, the odds ratios and 95% confidence intervals for the various AEDs relative to placebo for patients with >50% seizure reduction was 4.22 (2.80-6.35) for TPM, 2.32 (1.47-3.68) for LTG and 2.29 (1.53-3.43) for GBP; CLB was not included as it was not approved in the US. Since the confidence intervals for all these three overlapped, no significant differences regarding efficacy or tolerability were found.[24]

Our study suffers from a few drawbacks that it was not a randomized placebo controlled trial. Patients with all seizure types were included. The selection of the AEDs under study was also not random and there has also been a natural bias in selecting those with the most resistant seizures to receive TPM, as it was the latest among the new AEDs available when this study was done. The findings of our study are clinical observations and the limitations of such studies need to be considered while interpreting the results.

Cost wise, TPM and use of 2 new AEDs raised costs up to 4 times, LTG by 3 times and CLB doubled daily mean cost when added to existing conventional AEDs. The cost of new AEDs is an important factor for consideration when starting a patient on new AEDs, especially among populations in developing countries. Our results point to the use of the new AEDs sequentially: CLB, LTG and TPM in that order and then try a combination of two new AEDs if considered appropriate based on cost consideration.

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