

Effect of Antiepileptic drugs on Psychomotor Functions and Memory in Epilepsy Patients

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ABSTRACT

Objective: The present study was designed to compare the effect of various *antiepileptic drugs* on psychomotor and memory function in epileptic patient and to compare them with normal human volunteer. **Material & Methods:** It was cross-sectional case control study with a total of 30 cases and 30 controls. All 30 patients were diagnosed cases of Generalised Tonic Clonic Seizure (GTCS) and were on *antiepileptic drugs* for more than one year. Comparison of patients for all psychomotor tests with the normal subjects matching in age, gender and education was done using unpaired t test. **Results:** In all the test patients performed poor compared to control group and the difference was significant ($p < 0.05$) for Digit letter substitution test, Choice reaction time (audio and video) where as it was very significant ($p < 0.01$) for Critical flicker fusion test and PGI Memory Scale. In Six-letter cancellation test and Hand steadiness test also patients performed poor compared to subjects but difference was not significant. A further comparison of all the tests was done between patients on *monotherapy* and *polytherapy*. PGI Memory scale showed significantly ($p < 0.05$) inferior memory of patients on *polytherapy* as compared to *monotherapy*. In all other psychomotor tests also patients on *monotherapy* had better score compared to *polytherapy* but differences were not significant. **Conclusion:** Thus we conclude there is definitely a deterioration of psychomotor and memory with use of *antiepileptic drugs*.

Key words: Epilepsy, *Antiepileptic drugs*, Psychomotor, Memory, Cognition.

Key message: Literature suggests a possible link between *antiepileptic drugs* and negative consequences on memory and psychomotor function. The patients on *antiepileptic drugs* performed poor as compared to matching subjects for Digit letter substitution test, Choice reaction time (audio and video), Critical flicker fusion test and PGI Memory Scale. In Six-letter cancellation test and Hand steadiness test also patients performed poor compared to subjects but difference was not significant. Patients on *polytherapy* showed inferior memory in patients on *polytherapy* as compared to *monotherapy* by PGI Memory scale. In all other psychomotor tests also patients on *monotherapy* had better score compared to *polytherapy* but differences were not significant.

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INTRODUCTION

Epilepsy is a chronic disorder characterized by recurrent seizures, which may vary from a brief lapse of attention or muscle jerks, to severe and prolonged convulsions.¹ *Antiepileptic drugs* (AEDs) either as *monotherapy* or as *polytherapy* are efficacious in treatment of epilepsy. Studies have demonstrated that *antiepileptic drugs* affect cognition which may range from subtle to the more prominent features in epileptic patients.² Phenytoin, sodium valproate, phenobarbitone and *carbamazepine* are the most commonly used *antiepileptic drugs*. Phenytoin is implicated in dose-related decline in concentration, memory, visuomotor functions and mental speed, as well as generating anxiety, aggression, fatigue, and depression. Sodium valproate can impair concentration, complex decision making, as well as visuomotor function. Studies suggest that the disease as well the treatment reduce psychomotor function.³ In addition, a selection of case reports describe reversible parkinsonism and cognitive impairment with chronic use of valproic acid ('valproate encephalopathy'). More recent data denotes that phenobarbital have the greatest behavioral toxic potential with dose related impairment in attention and reaction time, performance IQ and short-term memory, as well as inducing a hyperkinetic syndrome in children. Studies in past have demonstrated decrements in performance of a series of simple psychomotor tests in epileptic patients receiving a supplemental *carbamazepine* dose. Patients with epilepsy who require high *carbamazepine* concentrations for optimal

control of seizures may be at risk of concurrent impairment of psychomotor function.⁴

The temporal lobe of the brain is important in consolidating memory and language abilities. Patients with chronic temporal lobe epilepsy often have problems with their language and memory abilities because the epilepsy disrupts these functions.⁵ Cognitive function of the brain is the ability to acquire process, integrate, store, and retrieve information. Psychomotor function includes sensorimotor processes such as reaction time and sensorimotor accuracy. Disturbance in these processes leads to patient maladjustment and may impair psychomotor performance, which plays important role in driving and operating complex machinery. Several factors like seizures frequency, etiology and seizure duration have potential effect on cognitive function in patients of epilepsy.⁶

Although the literature suggests a possible link between AEDs and negative consequences on memory and psychomotor function, epilepsy itself may also affect memory and psychomotor functions. Memory and psychomotor functions may also vary with age, gender and education level which work as confounding factors, and hence needed to be matched while selecting controls for the study. So this first case-control study was done to study effect of such antiepileptic drug on psychomotor functions and memory done at a tertiary care hospital.

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MATERIALS & METHODS

This cross-sectional case control analysis was conducted at *Neuromedicine* O.P.D and Department of Pharmacology, Civil Hospital Ahmedabad for duration of 10 month. Prior permission to conduct the study was obtained from Head of Unit, Department of *Neuromedicine* and approval was also obtained from the Institutional Ethics Committee (IEC) [IEC/Certi/154/14]. An informed written consent was obtained from all patients and volunteers before enrollment in the study.

Case-control study design

CASES - The investigator visited the OPD on Tuesday and Friday every week from 9:00 am to 1.00 pm. Patients aged 18-65 years of either gender, willing to participate and who gave consent with minimum education of 5th standard in Gujarati or Hindi or English and patient receiving single or multiple *antiepileptic drugs* for a minimum period of 1 year were included.

Patients of drug resistant epilepsy [Drug resistant epilepsy may be defined as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as *monotherapies* or in combination) to achieve sustained seizure freedom], patients suffering from any disease known to affect memory and psychomotor functions (e.g. Depression, Alzheimer's disease, schizophrenia, stroke, mental retardation, Parkinsonism),^{7,8} patients on any drug (s) known to affect memory and psychomotor functions. (Eg. H₁ blocker, β -blocker, anti-depressant, statins, anti-psychotics, hypnotics and sedatives), history of alcohol or any substance abuse and any other chronic disease and pregnant and lactating women were excluded from the study.

CONTROLS - A representative sample of 30 cases were matched with 30 controls and enrolled for the study. The controls for the study were selected after matching age, sex and education level with cases. All controls were selected according to same inclusion and exclusion criteria used for cases except that they were healthy human volunteers without epilepsy.

The data like demographic details, clinical examinations, any concomitant diseases and drug therapy, details of the drug treatment, were recorded in a pre designed Case Record Form (CRF). The patients as well as volunteers were then subjected to following tests to evaluate their psychomotor performance and memory:

Test of perception - Six-letter cancellation test (SLCT):⁹ Patients/Volunteers were required to cancel as many target digits as possible in a sheet consisting of randomized digits in 90 sec. The letter cancellation was carried out in a horizontal, vertical, or randomized manner by selecting any particular key letter. Net score was then calculated as total cancellations attempted minus wrong cancellations.

Test for recognition and recoding - Digit letter substitution test (DLST):¹⁰ Patients/Volunteers were required to insert the corresponding alphabet in the space above each digit in a sheet consisting of randomized digits in 1 min. The letter substitution was undertaken in horizontal, vertical or randomised manner by selecting a particular digit. Net score was calculated as total substitution attempted minus wrong substitutions.

Test for central integration - Critical flicker fusion test (CFFT):¹¹ It is a reliable psychometric test as there is no learning curve effect.¹² The critical fusion frequency was determined by increasing the frequency from 5 Hz till a steady light source was seen and the critical flicker frequency by decreasing the frequency from 50 Hz till flickering was seen. The final reading was an average of all the readings.

Motor component -

- Test for steadiness:**¹³ This is tested by steadiness tester, which consists of holes of different sizes and subjects has to insert stylus into the hole without touching its sides. The error was counted when the

stylus touches the walls of hole. Three readings were taken and final reading was an average of all the readings.

- Choice reaction time:**¹⁴ This test is performed on choice reaction time apparatus. There are 2 bulbs of different colours in the apparatus. The bulb is lighted by the investigator by pressing the switch on his side. The volunteer sitting on the opposite side is asked to extinguish the light by pressing the switch on his side. The reaction time required to switch off the light is noted. Three readings are taken and the average of the three is taken as the final reading. For audio component, initially, the volunteer will be conditioned to the two sounds and their corresponding switches. The investigator will press the switch on his side and the time required to recognise the sound and switch off the sound is noted. For each reaction total reaction time are obtained. Three readings are taken and the average of the three is taken as the final reading

Memory testing - PGI Memory Scale (PGIMS):¹⁵ It has ten different subtests to assess various parameters of memory (e.g. remote memory, recent memory, delayed recall). It is a simple pen and paper test, which can be easily performed in clinical ward or OPD. It takes 20-30 minutes to complete the tests. Overall score range between 0 to 100.

Statistical analyses: The data was recorded in Microsoft Excel Worksheet version 2007. The statistical evaluation was done using Graph Pad Demo version software. Unpaired t test and One-way ANOVA test was used to compare between two groups and more than two groups respectively. $p < 0.05$ was considered to be statistically significant.

RESULTS

Patient characteristics

This cross sectional study at a tertiary care teaching hospital was done with the aim to see the effect of *antiepileptic drugs* on memory and psychomotor functions as compared to healthy controls. The study included a total of 30 cases and 30 controls. All 30 patients were diagnosed cases of Generalised Tonic Clonic Seizure (GTCS) and were on *antiepileptic drugs* for more than one year. Out of 30 patients 18(60%) were males and 12(40%) females. The average age and weight of patients were 30.2±9.83 years and 50.43±6.47 kg respectively. Out of 30 patients 20 (66%) had education below or up to secondary level, 02(6.6%) till higher secondary and remaining 08(26.6%) were graduates. Upon matching, cases and controls matched in 1:1 ratio based on age, gender and education. The average year of treatment with ADEs was 3.2±2.46 years and all patients were on stable therapy having no history of seizure in last 6 months. (Table 1)

To test whether chronicity of disease itself had any effect on psychomotor and memory cases were compared by dividing the patients according to the duration of epilepsy. They were grouped as: 1-2 year (n=12), 2-3 year (n=07) and >3 (n=11) year of disease. Values of all the tests performed were expressed as mean ± S.E.M. Comparison between various duration group was done using One-way ANOVA test and P value < 0.05 was considered as significant. (Table 2)

Table 1: Demographic and Clinical characteristics

Variable	Case (n=30)	Control (n=30)
Male: Female	18:12	18:12
Age (years) (mean±SD)	30.2±9.83	29.7±9.45
Weight (Kg) (mean±SD)	50.43±6.47	51.06±6.38
Education		
1) ≥Secondary	20	20
2) Higher secondary	02	02
3) Graduate	08	08

Table 2: Comparison of Psychomotor and Memory at different durations of epilepsy

Test	1-2 years	2-3 years	>3 years
	(n=12) mean ± S.E.M	(n=07) mean ± S.E.M	(n=11) mean ± S.E.M
Six-letter cancellation test (SLCT)	26.58±5.53	28.87±5.30	28.36±4.36
Digit letter substitution test (DLST)	26.54±4.72	25.12±5.10	26.11±4.87
Critical flicker fusion test (CFFT)	42.08±1.44	43.21±1.22	42.72±1.75
Hand steadiness test	48.17±11.49	50.14±11.19	51.01±10.44
Choice reaction time – Audio	1.54±0.27	1.44±0.25	1.47±0.31
Choice reaction time – Visual	1.47±0.17	1.59±0.21	1.60±0.19
PGI Memory Scale (PGIMS)	60.00±2.76	62.42±2.67	63.18±3.76

Note: Test used - One-way ANOVA

No significant difference (p>0.05) between disease duration groups

Table 3: Comparison of Psychomotor and Memory between Monotherapy and Polytherapy

Test	Monotherapy (n=14)	Polytherapy (n=16)	P value
	mean ± S.E.M	mean ± S.E.M	
Six-letter cancellation test (SLCT)	28.28±1.16	27.00±1.48	0.50
Digit letter substitution test (DLST)	26.57±1.13	25.56±1.42	0.59
Critical flicker fusion test (CFFT)	42.85±0.44	42.34±0.35	0.37
Hand steadiness test	48.42±2.61	50.50±2.55	0.57
Choice reaction time – Audio	1.47±0.07	1.50±0.06	0.73
Choice reaction time – Visual	1.52±0.04	1.56±0.03	0.52
PGI Memory Scale (PGIMS)	63.07±0.92	60.56±0.74	0.04*

Note: Test used – Unpaired t test

*Significant difference (p<0.05) between monotherapy and polytherapy

Table 4: Dose range and average dose

Drug (Number of patients)	Dose Range Prescribed (mg)	Average Dose (Mean ± SEM)
Sodium valproate (17)	600 – 1200	976.47 ± 56.57
Phenytoin (18)	200 – 400	288.88 ± 7.62
Carbamazepine (5)	400 – 1200	720 ± 135.65
Phenobarbital (6)	60 – 120	90 ± 7.74

Among various groups almost similar results were obtained for all the tests performed and no significant difference was seen when comparison was done using one way ANOVA. Another comparison between patients on monotherapy (14) and polytherapy (16) was done using unpaired t test. Values of all the tests performed were expressed as mean ± S.E.M. P value < 0.05 was considered as significant. (Table 3)

As seen in table 3 PGI Memory scale showed significantly (p<0.05) inferior memory of patients on polytherapy as compared to monotherapy. In all other psychomotor tests also patients on monotherapy had better score compared to polytherapy but differences were not significant.

Monotherapy was prescribed in 14 patients out of which 07 were on valproate, 04 on phenytoin and 03 on carbamazepine. Polytherapy was given in 16 patients of which most common combination was valproate + phenytoin (08 patient) followed by phenytoin + phenobarbital (and carbamazepine + valproate (02 patient). Before evaluating effect of individual drugs on psychomotor and memory, range and average dose of all individual drugs prescribed to patients enrolled in the study was

tabulated. All drugs were found to be prescribed in the recommended dose range according to standard pharmacological textbooks. (Table 4)

A further comparison between individual drugs was done. Values of all the tests performed are expressed as mean ± S.E.M. All drugs produced similar results with no individual drug or particular combination better than other. (Table 5)

The effect of antiepileptic drugs on psychomotor and memory was assessed by various tests performed both on patients as well as on normal subjects. Values of all the tests performed were expressed as mean ± S.E.M. Comparison with the normal subjects was done using unpaired t test. P value < 0.05 was considered as significant. (Table 6)

In all the patients the values of the test were performed poor compared to matching controls and the difference was significant (p<0.05) for DLTS, Choice reaction time (audio and video) where as it was very significant (p<0.01) for CFFT and PGIMS. In SLCT and Hand steadiness test also patients performed poor compared to subjects but difference was not significant.

Table 5: Mean score of individual drugs and combinations

DRUG	Six-letter cancellation test (SLCT)	Digit letter substitution test (DLST)	Critical flicker fusion test (CFFT)	Hand steadiness test	Choice reaction time – Audio	Choice reaction time – Visual	PGI Memory Scale (PGIMS)
Sodium valproate (07)	27.96±1.25	26.63±1.17	42.16±0.49	49.06±2.53	1.42±0.08	1.58±0.05	62.86±0.98
Phenytoin (04)	28.57±1.19	26.51±1.18	43.14±0.47	48.12±2.67	1.51±0.09	1.46±0.04	63.27±0.97
Carbamazepine (03)	28.44±1.30	26.49±1.14	42.96±0.42	48.08±2.65	1.50±0.07	1.44±0.05	63.14±0.94
Valproate + Phenytoin (08)	26.84±1.55	25.60±1.51	42.12±0.38	50.65±2.61	1.40±0.07	1.51±0.04	61.24±0.81
Phenytoin + Phenobarbital (06)	27.12±1.52	25.52±1.37	42.49±0.32	50.36±2.63	1.60±0.08	1.59±0.03	60.22±0.83
Carbamazepine + Valproate (02)	27.20±1.41	25.48±1.44	42.37±0.34	50.30±2.52	1.52±0.07	1.60±0.04	60.31±0.71

Table 6: Comparison of Psychomotor and Memory between Case and Control

Test	Case (n=30) mean ± S.E.M	Control (n=30) mean ± S.E.M	p-value
Six-letter cancellation test (SLCT)	27.60±0.95	29.70±0.78	0.094
Digit letter substitution test (DLST)	26.03±0.91	28.93±0.73	0.016*
Critical flicker fusion test (CFFT)	42.50±0.26	43.66±0.26	0.0028**
Hand steadiness test	49.53±1.80	48.10±1.70	0.56
Choice reaction time – Audio	1.49±0.04	1.35±0.04	0.036*
Choice reaction time – Visual	1.54±0.02	1.40±0.04	0.012*
PGI Memory Scale (PGIMS)	61.73±0.61	64.20±0.64	0.0077**

Note: Test used – Unpaired t test

*Significant difference (p<0.05) between case and control

**Very significant difference (p<0.01) between case and control

DISCUSSION

Epilepsy is a chronic disorder which needs lifelong treatment with *Antiepileptic drugs* (AEDs) either as *monotherapy* or as *polytherapy*. As epilepsy is produced by widespread and uniform process within the cortex of the brain, epilepsy itself may effect memory and psychomotor functions. Although the literature suggests a possible link between AEDs and negative consequences on memory and psychomotor function, a very few studies test a hypothesis of a specific association. So this first case-control study was done to study effect of such antiepileptic drug on psychomotor functions and memory done at a tertiary care teaching hospital.

The average age of patients in our study was 30.2±9.83 years This is similar to a study conducted in Malaysia¹⁶ that reported a mean age of patients of epilepsy to be 31.8±11 years. However, observations made in Brazil¹⁷ and South India,¹⁸ reported that the mean age of patients suffering from epilepsy to be 43.86 ±13.98 and 34.89 ± 9.22 years respectively. In our study 60% were males while remaining 40% females which is to studies done in Ethiopia¹⁹ and South India. In our study 66% of patients had education till secondary level while remaining 33% had higher education. One of the Indian study also showed similar results where 77% of patients were either primary or secondary education and the remaining 23% had higher education.

In our study the duration of disease did not show any significant difference in psychomotor skills as well as memory of patients suffering with epilepsy. The possible reason is, we had enrolled only those patients who were stable with no seizure attack in last six month. It also showed that if epilepsy is well controlled with ADEs chronicity of disease didn't

affect memory and psychomotor skills. One more observation made in our study was significant deterioration of memory in patients on *polytherapy* as compared to *monotherapy*. In all other psychomotor tests also patients on *monotherapy* had better score compared to *polytherapy* but differences were not significant. Similar to our study Gillham et al, 1991²⁰ also observed that *polytherapy* group had worse effect on memory and psychomotor function than *monotherapy* and controls for decision and choice reaction time. A Ethiopian study also reported that *polytherapy* offers no advantage over *monotherapy*.²¹ Thus increase in the number of AEDs effect memory and psychomotor skills by suppressing neuronal excitability or enhancing inhibitory neurotransmission.

To further confirm the effect of AEDs on memory and psychomotor skills we did a comparison of our patients with healthy volunteers matching in age, gender and education level as these are the confounding factors also effecting memory and psychomotor skills. No significant difference between patients and healthy volunteers was seen in SLCT which tests a person's ability of perception and attention. But a significant deterioration among patients was seen in Digital letter substitution test which also tests perception and attention. Overall it indicates that AEDs deteriorate level of perception and attention. Hand steadiness test which tests for motor component produced similar results in both case and control groups. It indicates that AEDs don't deteriorate motor coordination. But a significant deterioration among patients was seen in critical flicker fusion test, Choice reaction time both of which tests cognition, central integration. It indicates that AEDs also lowers the level of cognition and central integrity. PGIMS which is used specifically to test memory was also deteriorated to a great deal with the use of AEDs in patients compared to controls. Similar results were observed by Craig-Tallis et al, 1994²²

where decrement in cognitive function and reaction time was seen with use of AEDs. But contrary to our finding Craig Tallis study showed improvement in memory. Study done by Meador *et al*, 2003²³ for sodium valproate showed cognitive impairment as compared to placebo. Study done by Sun *et al*, 2008²⁴ reports no increase in reaction time with little evidence of attentional impairment. At the same time there are studies which observed no deterioration of cognition with use of AEDs (Spitz *et al*, 1991)²⁵

Our study indicates that patients of epilepsy which are treated with antiepileptic drugs have poor psychomotor skills as well as memory as compared to general population. Amongst all the antiepileptic drug studies show that Phenobarbital shows maximum dose related behavioral toxic potential. Study by Cavanna AE shows that phenytoin declines memory, concentration, visuomotor functions and mental speed. The active metabolite of carbamazepine i.e. carbamazepine epoxide is at least partially responsible for cognitive and psychomotor effect. Valproic acid also impairs concentration and complex decision making and vasomotor function.²⁶ This deterioration can be attributed to disease itself or antiepileptic drugs or both. But since only those patients were enrolled in whom disease was well controlled and chronicity of disease didn't show any change in psychomotor skills and memory, contribution of disease in deterioration of psychomotor and memory seems less likely. It is more likely due to use of antiepileptic drugs and use of polytherapy further deteriorates the condition. Hence, we can conclude that antiepileptic drugs i.e. phenytoin sodium valproate, and carbamazepine, along with other drugs used in combinations effect perception, attention, cognition, central integration as well as memory. The effect was more in patients who were on polytherapy than monotherapy.

However, there were few limitations in our study. We used a less number of patients, newer AEDs were not evaluated as ours is government hospital where newer AEDs are not available and children were not enrolled in whom memory and psychomotor skill are in developmental phase and are more likely to get effected by use of AEDs.

CONCLUSION

As our study and most other study point out that there is definitely a deterioration of psychomotor and memory with use of AEDs, and hence this component should be considered while prescribing drug therapy. Further if the epilepsy is well controlled an attempt toward tapering of drug therapy to minimum level can improve memory and psychomotor functions. This will help epilepsy patients to perform more skilful jobs and thus improving their quality of life also.

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CONFLICT OF INTEREST

There are no conflicts of interest.

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