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Original Research Article

Neuropsychological side effects of anti-epileptic drugs in epilepsy patients: a cross sectional study

Namratha M. V.[1], Anuradha H. V.[1]* Mahendra J. V.[2]

[1]Department of Pharmacology, M S Ramaiah Medical College and Hospital, Bengaluru, Karnataka, India
[2]Department of Neurology, M S Ramaiah Medical College and Hospital, Bengaluru, Karnataka, India

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***Correspondence:**
Dr. Anuradha H. V.,
Email: dranuradhapharmac@gmail.com

ABSTRACT

Background: Epilepsy is the fourth most common neurological disorder in world. Managing an epilepsy with anti-epileptic drugs (AEDs) either as monotherapy or polytherapy is necessary to reduce the deleterious effect of the disease and to provide neuroprotection. AEDs exert their negative effects on cognition by suppressing neuronal excitability or enhancing inhibitory neurotransmission. These neuropsychological side effects are found to be modest when the drug level is within the therapeutic concentration and used as monotherapy. Objectives were to assess the prevalence of neuropsychological side effects among epilepsy patients who were on antiepileptic drug therapy.
Methods: An open label, cross-sectional, clinical study was conducted at a tertiary care hospital, 126 participants were recruited. Participants demographic data, detailed medical and seizure history followed by neuropsychological tests was performed. The prevalence was assessed based on the number of participants scoring <15th percentile in one or more tests.
Results: Out of 126 participants who were recruited, 82 participants were on monotherapy and 44 participants were on polytherapy. Levetiracetam was the most commonly prescribed drug as monotherapy, followed by phenytoin, carbamazepine and valproate; whereas in polytherapy levetiracetam, clobazam followed by phenytoin were the commonly prescribed AED. The most common adverse effect was drowsiness, followed by headache, hypersensitivity reaction, giddiness, tremors, anxiety etc. The prevalence of neuropsychological side effects was 77.8%. The prevalence of impairment between monotherapy and polytherapy was statistically insignificant (p=0.727).
Conclusions: In this study, levetiracetam was the most commonly prescribed drug and the most common adverse effect was drowsiness due to AEDs. The subgroup analyses between monotherapy and polytherapy did not show any statistically significant neuropsychological impairment when compared based on the gender, age groups, duration of epilepsy with medication and duration of current therapy.

Keywords: Antiepileptic drug, Cognition, Epilepsy, Neuropsychological side effects

INTRODUCTION

Epilepsy being the fourth most common neurological disorder in the world, is characterized by unpredictable and recurrent occurrence of seizure.[1] Managing an epilepsy patient to have a seizure free life using AED is necessary in order to reduce the deleterious effect of the disease and to provide neuroprotection.[2] Patients are treated either with monotherapy (one AED) or polytherapy (two or more AEDs). The disease itself and its treatment with AEDs might show some deleterious effect on cognition and behaviour which in turn contributes for a higher prevalence of neuropsychological dysfunction among affected individuals than the general population. Some of the underlying influencers for this kind of impairment are anti-epileptic drug therapy, underlying neuropathology, neuronal discharges during ictal and interictal period and psychosocial issues.[3]

The pharmacokinetic and pharmacodynamic factors in individuals older than 65 years and the developing nervous system in children make them more susceptible for the long-term AED induced cognitive impairment.[4,5] According to various studies, the different types of antiepileptic drugs having different mechanism of action are shown to have various side effects, out of which neuropsychological side effects are one among them. These neuropsychological side effects are found to be modest when the drug level is within the therapeutic concentration and in monotherapy. Hence, frequent individual neuropsychological assessment of an epilepsy patient is necessary to change the treatment regimen when the patient experiences a significant neuropsychological disturbance in order to reduce the further decline in quality of life of the patient due to neuropsychological effect of AEDs. This study was done as there were very limited number of studies been undertaken regarding the association between antiepileptic drugs and its neuropsychological side effects in India.

Objectives

Objectives were to assess prevalence of neuropsychological side effects of AEDs in epilepsy patients and to compare the neuropsychological side effects of the monotherapy and polytherapy in the epilepsy patients.

METHODS

Procedure

This open label, cross-sectional clinical study was conducted to assess the neuropsychological side effects of anti-epileptic drug therapy in epilepsy patients who visited epilepsy clinic at department of neurology, M. S. Ramaiah medical college and hospitals from January 2018 to December 2018 for a period of one year after obtaining approval from the ethics committee of the institution (Ref: SS-1/EC/012/2017). A written informed consent was taken from each patient who was willing to participate in the study.

Inclusion criteria

Patients aged between 18 to 65 years diagnosed with epilepsy and on regular treatment with stable doses of AED for minimum of 3 months, epilepsy patients on AED therapy with seizure free period minimum of 1 month and patients willing to give written informed consent were included in study.

Exclusion criteria

Patients with head injury, patients diagnosed with other neurological diseases and psychiatric diseases, patients diagnosed with chronic renal and hepatic diseases and patients diagnosed with chronic debilitating conditions like malignancy were excluded from study.

The data which were collected from the recruited patients include demographic details, detailed medical history and clinical examination of the patient including IQ (Wechsler adult intelligence scale-IV), IQ<70 was considered as mental retardation, seizure history (Age of onset of seizure and family history, duration of epilepsy and type and duration of AED therapy and its regimen) and cognitive assessment:[6,7]

Tests used in the assessment of neuropsychological side effects were as follows: Memory-Rey's auditory verbal learning test (RAVLT), Rey's visual memory test and verbal working memory by Smith and Jonides, psychomotor slowing-Finger tapping test (FTT) by Spreen and Straws, attention-sustained attention test by Lezak, category fluency test (CFT) by Lezak, cognitive flexibility-Wisconsin card sorting test (WCST) by Milner, mental speed- digit symbol substitution test (DSST) and response inhibition-Stroop test.

Sample size justification

Based on the previous study conducted by Joshi et al it was found that percentage of memory problem in monotherapy was known to be 30.3% and in present study, sample size was calculated based on this expected proportion, considering the absolute precision of 8% and desired confidence level of 95%, which was calculated to be 126.

Statistical methods

All the quantitative variables were summarized using descriptive statistics. All the qualitative variables like the type of therapy, side effects, adverse drug reactions etc was presented using frequency and percentage. Chi square test was used to test for the difference in proportion between the different types of therapy and the side effects associated with it. The interpretation of these quantitative scores was based on percentiles and scores less than 15th percentile is considered as deficient scores.[6] The prevalence of neuropsychological side effects was analysed based on the number of patients scoring <15th percentile (neuropsychologically impaired or deficit) in one or more tests of the neuropsychological test battery.[8] P<0.05 is considered statistically significant. All analyses were performed using SPSS software version 18.0.

RESULTS

Total of one hundred and twenty-six (126) participants diagnosed with epilepsy, on antiepileptic drug therapy visiting the epilepsy clinic, at the department of neurology were recruited based on inclusion criteria. The baseline demographic data of the enrolled patients has been depicted in Table 1.

In this study, totally 6 different AED groups and eleven different antiepileptic drugs prescribed including both older and newer AEDs. Newer AEDs mainly levetiracetam was the most commonly prescribed drug among

monotherapy. Other commonly prescribed drugs in descending order of their prescription frequency were phenytoin, clobazam, carbamazepine, sodium valproate, oxcarbazepine, phenobarbitone, lacosamide, topiramate and zonisamide. Among polytherapy prescriptions, levetiracetam, clobazam followed by phenytoin were frequently prescribed AEDs.

Table 1: Baseline characteristics of the participants.

Baseline characteristics	N
Age (in years)	
Age range	18-65
Mean ± standard deviation (SD)	33±12.8
Gender distribution, n (%)	
Male	70 (55.6)
Female	56 (44.4)
Total number of patients, n (%)	
Monotherapy	82 (65.1)
Polytherapy	44 (34.9)
Duration of epilepsy with medication (years), mean ± SD	7.2±7.1
Duration of current therapy (months), mean ± SD	13±12.2
Number of patients on concomitant medications, n (%)	20 (15.87)
MMSE (Mean ± SD)	29.96±0.26

Twenty participants had co-morbidities for which eight different groups of drugs were prescribed. The commonly prescribed groups of drugs were antihypertensive drugs (amlodipine, nebivolol, telmisartan), followed by antiplatelet drugs (aspirin, clopidogrel), hypolipidemic drugs (atorvastatin), thyroxine, antidiabetic drugs (metformin, glimepiride, insulin), anticoagulants (warfarin), folic acid and antitubercular drugs.

Primary objective of the study was to assess prevalence of neuropsychological side effects of antiepileptic drugs in epilepsy patients. It was analysed based on the number of participants showing impairment (score <15th percentile) in one or more tests of the neuropsychological test battery. Based on this, participants were grouped as either normal or impaired. In this study, there were 28 (22.2%) participants who scored above 15th percentile in all the tests and 98 (77.8%) participants who scored less than 15th percentile in at least one test. The prevalence of neuropsychological side effects in this study was 77.8% (Figure 1), which was slightly higher than 73% as depicted in a study conducted by Tanner-Eggen et al to analyse prevalence of low scores for neuropsychological test battery among healthy volunteers.[8]

The secondary objective of this study was to compare the neuropsychological side effects of monotherapy and polytherapy in epilepsy patients. In this study, participants on AEDs have experienced adverse effects like drowsiness (36) followed by headache (8), hypersensitivity reaction, giddiness, tremors, and anxiety etc., (Figure 2). According to study conducted by Ortinski et al some of the most commonly observed cognitive side effects among patients taking AEDs are sedation, somnolence, distractibility, insomnia and dizziness.[9] Sedation in particular was the most commonly associated cognitive side effect among most of AED therapies.[9] Frequency of adverse effects between monotherapy and polytherapy were not statistically significant (p=0.067, 0.355 and 0.511 for drowsiness, headache and other side effects respectively) (Table 2).

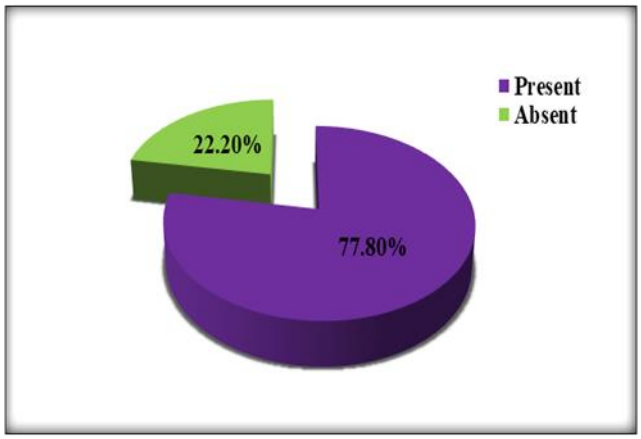

Figure 1: Prevalence of neuropsychological side effects.

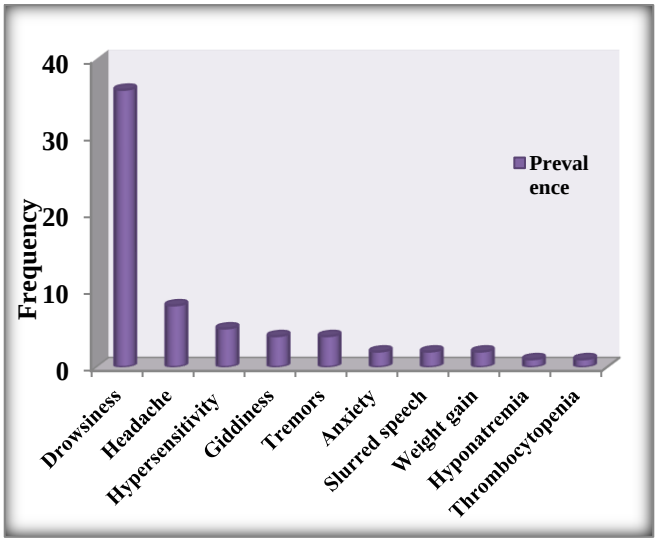

Figure 2: Pattern of side effects for antiepileptic therapy.

Number of participants with normal scores was slightly higher in monotherapy group compared to polytherapy (Table 3), which implies that the participants' showing impairment was slightly lesser in the monotherapy group than the polytherapy group (Table 3); whereas percentage of participants showing neuropsychological impairment was shown for different tests for monotherapy and polytherapy has been represented in Table 4 and showed polytherapy had higher prevalence of impairment in all the cognitive tests except in digit vigilance test and Stroop test.

Table 2: Therapy based frequency distribution of adverse effects.

Therapy	Drowsiness, n	Headache, n	Others, n
Monotherapy	19 (Levetiracetam-18) (Clobazam-1)	4 (Levetiracetam-1), (Phenytoin-2) (Valproate-1)	13
Polytherapy	17	4	8
Total	36	8	21
P value	0.067	0.355	0.511

Table 3: Number of participants with normal and low scores in each of the performed cognitive tests based on monotherapy and polytherapy.

Test name	Interpretation	Monotherapy total, n=82	Polytherapy total, n=44	P value
DSST	Normal	72	35	0.217
	Deficit	10	9	
Fluency test	Normal	68	37	0.867
	Deficit	14	7	
Vigilance test	Normal	71	38	0.972
	Deficit	11	6	
Verbal 1 back test	Normal	68	36	0.876
	Deficit	14	8	
Verbal 2 back test	Normal	71	36	0.476
	Deficit	11	8	
RAVLT	Normal	70	35	0.403
	Deficit	12	9	
CFT- IR	Normal	67	35	0.768
	Deficit	15	9	
CFT-DR	Normal	72	31	0.016
	Deficit	10	13	
FTT-right	Normal	59	31	0.859
	Deficit	23	13	
FTT-left	Normal	37	19	0.835
	Deficit	45	25	
WCST	Normal	73	35	0.350
	Borderline	3	3	
	Deficit	6	6	
Stroop test	Normal	62	37	0.269
	Deficit	20	7	

Table 4: Percentage of patients showing impairment in the monotherapy and polytherapy.

Test name	Percentage (%) of patients showing the neuropsychological impairment		P value
	Monotherapy	Polytherapy	
DSST	12	20.5	0.217
Fluency test	17	15.9	0.867
Vigilance test	13.4	13	0.972
Verbal 1 back test	17	18.2	0.876
Verbal 2 back test	13	18	0.476
RAVLT	14.6	20.5	0.403
CFT-IR	18.3	20.5	0.768
CFT-DR	12.2	29.5	0.016
FTT-right	28	30	0.859
FTT-left	54.9	56.8	0.835
WCST	11	20.2	0.350
Stroop test	24	15.9	0.269

According to a study conducted by Ortinski et al the cognitive deficits often seem to be modest among monotherapy patients unlike polytherapy patients or those with high AED levels in blood, who are at a higher risk of cognitive deficit.[9] The observed prevalence of neuropsychological impairment between monotherapy and the polytherapy was not statistically significant (p=0.727).

The percentage of participants showing impairment was found higher in all the age groups as shown in the Figure 3; but slightly more in the age group of 31 to 40 years. This observed that the impairment among different age groups was not statistically significant (p=0.886). The comparison of prevalence of impairment between males and females showed higher prevalence in males but was not statistically significant (p=0.270) as shown in Figure 4.

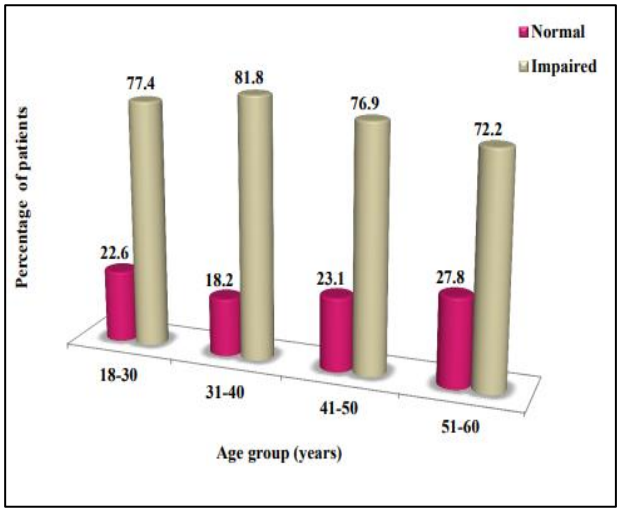

Figure 3: Age group-based distribution of neuropsychological test results.
Neuropsychological impairment among age groups was not significant (p=0.886).

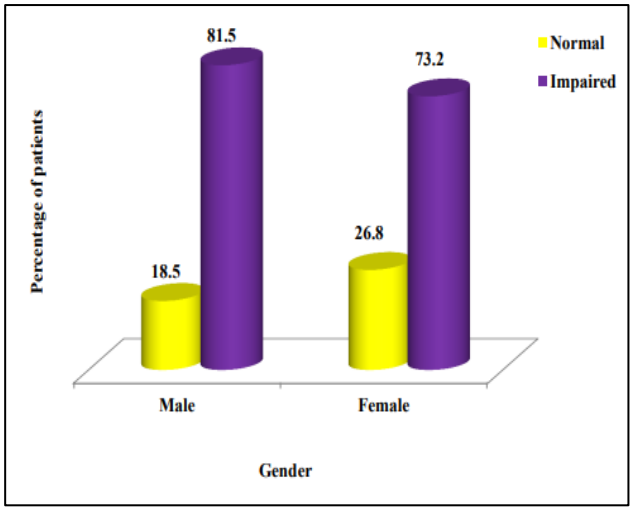

Figure 4: Gender wise neuropsychological test result distribution, (p=0.270).

DISCUSSION

Antiepileptic drugs not only act by enhancing inhibitory neurotransmission and suppressing neuronal excitability; they also act by impairing the release of neurotransmitters, enzymes, and other factors which are critical for information processing and memory.[10] These actions in turn produce global changes at the level of neuronal excitation in the CNS and often results in cognitive and behavioural deficits. Hence, the major concern lies in choosing an appropriate drug and its dose to obtain the necessary control on seizures. In this study, the most commonly used anti-epileptic drug was levetiracetam. Levetiracetam is safe and efficacious. Studies have shown that the drug levetiracetam does not cause cognitive impairment in healthy volunteer or in epilepsy patients.[11,12] In a study conducted by Koo et al to estimate the effect of levetiracetam monotherapy on cognition and mood in epilepsy patients versus healthy volunteers, showed that long-term monotherapy with levetiracetam improved the cognitive performance of epilepsy patients.[13] Also, improvement in various cognitive domains like attention, mental flexibility, psychomotor speed, verbal fluency and executive function was observed in levetiracetam monotherapy group.[13]

In a study conducted by Helmstaedter et al the cognitive improvement in 58% of patients was observed after introducing levetiracetam as monotherapy or as an add on therapy.[14] Another study conducted by Zhou et al to evaluate the effect of levetiracetam as an add on drug on quality of life as well as cognition in refractory epilepsy patients.[15]

These cognitive and behavioural deficits display inter individual variation and must be considered independently for each patient.[10] A study conducted by Tanner-Eggen et al showed that having a low neuropsychological test scores among healthy population was common.[8] In addition, from a study conducted by Brooks et al. it was observed that the prevalence of low scores for the neuropsychological tests varied by the education level of the examinee.[16] Hence it is important to consider the psychometric principle which says that the number of low scores varies by the demographic data of the subject and emphasis on the education level of the subject is important because lesser the education, greater the number of low scores.[16]

Limitations

Apart from antiepileptic drugs, there are many other confounding factors that can influence the cognitive function of an epilepsy patient like duration of the disease, seizure frequency, age of onset, type of seizure, nature of pathology etc. Similarly, education level of the patient indirectly influences the cognitive test scores. These confounding factors were not considered. Considering some improvisations in the study design either by adding a normal control group or by making it as prospective

study might help in obtaining a detailed effect of drug on cognition.

CONCLUSION

Epilepsy being the fourth most common neurological disorder in world and is characterized by unpredictable and recurrent occurrence of seizure. The mainstay of epilepsy management is anti-epileptic drug therapy. In this study, newer AEDs especially levetiracetam was the most commonly prescribed drug. As monotherapy, levetiracetam was more commonly prescribed than phenytoin, carbamazepine and valproate. In polytherapy levetiracetam, clobazam followed by phenytoin were the commonly prescribed AEDs. The subgroup analyses did not show any statistically significant neuropsychological impairment when compared based on the gender, age groups. Participants showing neuropsychological impairment in each of the cognitive tests between monotherapy and polytherapy was statistically insignificant.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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