***International Journal of Pharmacological Research***
ISSN: 2277-3312 (Online)
Journal DOI: https://doi.org/10.7439/ijpr **Research Article**

# Evaluation of effect of newer antiepileptic drugs (Lamotrigine and Zonisamide) on cognitive performance in patients of epilepsy

**Anup Bharati**[1], Rohan Hire[2*], Parag Kinge[3], Tushar Bagle[4] and Pooja Bagle[5]

[1]*Associate Professor, Department of Psychiatry, NDMVP's VPMC Nashik, Maharashtra, India – 422003*
[2]*Assistant Professor, Department of Pharmacology, RGMC & CSMH, Thane, Maharashtra, India – 400605*
[3]*Sciformix Technologies Pvt. Ltd. Pune, Maharashtra, India – 411057*
[4]*Associate Professor, Department of Pharmacology, RGMC & CSMH, Thane, Maharashtra, India – 400605*
[5]*Assistant Professor, Department of Biochemistry, RGMC & CSMH, Thane, Maharashtra, India – 400605*

## Abstract

**Introduction:** Epilepsy, a disorder of unprovoked seizures is a multifaceted disease affecting individuals of all ages with a particular predilection for the very young and old. Epilepsy is one of the most common neurologic conditions, with an incidence of approximately 50 new cases per year per 100,000 populations. Impairment in cognitive function is a major influential factor on drug tolerability. Hence, we aimed at evaluating the effect of newer antiepileptic medicines (Lamotrigine and Zonisamide) on cognitive functions in patients who were seizure free for one year, in Western India.
**Material & Methods:** It was a prospective observational cohort study. Patients receiving newer antiepileptic medicines as monotherapy and satisfying the inclusion and exclusion criteria were included in this study. Evaluation of cognitive performance was done by using Addenbrooke's Cognitive Examination Revised [ACER] Questionnaire at baseline followed by three months and six months.
**Observation and Results:** Out of 51 enrolled patients, 39 completed the study. Newer AEDs Lamotrigine and Zonisamide had shown positive outcome on the cognitive performance for the parameters of attention, concentration, memory, verbal fluency, language and visuospatial skills.
**Conclusion:** As concluded by previous studies, it has been established that newer antiepileptic drugs like Lamotrigine and Zonisamide definitely improves baseline cognitive performance score. Further comparative studies with older antiepileptic drugs (AEDs) are needed to establish higher level of evidence.
**Keywords:** Lamotrigine, Zonisamide, Cognition, Epilepsy.

***Correspondence Info:**
Dr. Rohan Hire,
Assistant Professor,
Department of Pharmacology,
RGMC & CSMH, Thane, Maharashtra, India

***Article History:**
**Received:** 04/11/2020
**Revised:** 30/11/2020
**Accepted:** 30/11/2020
**DOI:** https://doi.org/10.7439/ijpr.v10i11.5537

**QR Code**

**How to cite:** Bharati A, Hire R, Kinge P, Bagle T, Bagle P. The Evaluation of effect of newer antiepileptic drugs (Lamotrigine and Zonisamide) on cognitive performance in patients of epilepsy. *International Journal of Pharmacological Research* 2020; 10(11): e5537. Doi: 10.7439/ijpr.v10i11.5537 Available from: https://ssjournals.com/index.php/ijpr/article/view/5537



## 1. Introduction

Epilepsy, a disorder of unprovoked seizures is a multifaceted disease affecting individuals of all ages with a particular predilection for the very young and old. In addition to seizures, many patients often report cognitive and psychiatric problems associated with both the seizures themselves and its therapy. Epilepsy has numerous etiologies both idiopathic and acquired with a wide range of therapeutic responses [1].

Epilepsy is one of the most common neurologic conditions, with an incidence of approximately 50 new cases per year per 100,000 populations. About 1% of the population suffers from epilepsy, and about one-third of patients have refractory epilepsy (i.e., seizures not controlled by two or more appropriately chosen antiepileptic medications or other therapies). Approximately 75% of epilepsy begins during childhood, reflecting the heightened susceptibility of the developing brain to seizures [2].

Drug tolerability of anti-epileptic medicines plays an important role in maintaining the treatment for longer period. The side effects profile is a major contributing factor for drug retention rates [3-7]. Although the causes of cognitive impairment in patients with epilepsy have not been completely elucidated, three factors are clearly involved: the underlying etiology of epilepsy, the effects of seizures themselves, and the central nervous system effects of antiepileptic drugs (AEDs). The older antiepileptic drugs acting through the GABAergic neurotransmission are particularly prone to produce modest but statistically significant disruption of cognitive processes. There are very few studies proving the improvement of cognitive functions by new generation anti-epileptic drugs (AEDs). This could be due to their non GABAergic mechanisms, as they influence the ion channels and glutaminergic transmission.8 However, mechanism of action of AEDs does not fully predict its cognitive / behavioural profile, as mechanism of action of the AEDs are only partially known and cognitive effects could be exerted by an unknown mechanism of action [8].

It's really difficult to measure the damage in cognitive function secondary to AEDs therapy for the patients of epilepsy. Many studies had been conducted, however, with many lacunaes which ultimately produced contradictory results without probable scientific explanation. Confusion still remains over the exact cognitive impact of older and newer generation AEDs as a group, as well as the individual medicines. Also, data from comparative studies is lacking in the Indian population and most of the times, the results of international studies are extrapolated in Indian patients.

Hence, we aim at evaluating the effect of newer antiepileptic medicines on cognitive functions in patients who were seizure free for one year, in Western India.

### 1.1 Aims and Objectives

To test the change in cognitive performance using standardized test in patients receiving newer (e.g. Lamotrigine, Zonisamide) antiepileptic medicines as monotherapy.

## 2. Materials & Methods

It was a prospective observational cohort study. Patients receiving newer antiepileptic medicines as monotherapy and satisfying the inclusion and exclusion criteria were included in this study. This study was conducted at the Psychiatry and Medicine outpatient department in a tertiary care teaching hospital from Western India. Inclusion Criteria were – 1) Patients on monotherapy with newer (either Lamotrigine or Zonisamide) antiepileptic medicine. 2) Patients having generalized tonic-clonic or partial seizures. 3) Patients who are seizure free for past one year. 4) Minimum educational level – Secondary School Certificate (SSC) pass. 5) Age: - 18-45 years of both gender and 6) Women ready to practice contraceptive measures during the study period. Exclusion Criteria were – 1) Past or family history of any psychiatric illness. 2) History of head injury or trauma or other brain pathology. 3) History of chronic systemic illness. 4) History of smoking, alcoholism, drug addiction and 5) Pregnant and lactating women. Patients shifting from monotherapy to polytherapy, patients shifting from one antiepileptic medicine to another and noncompliant patients were withdrawn from the study. The study was approved by the Institutional Ethics Committee. This was an observational study and patient allotment to different treatment groups was done by the treating physician. A written informed consent was taken from each patient after explaining them the nature of the study

Evaluation of cognitive performance was done three times – first at baseline which is at the time of allocation of patient to the treatment group. Second at three months of follow up and third at six months of follow up.

The Addenbrooke's Cognitive Examination Revised [ACER] Questionnaire was used to evaluate the cognitive performance of antiepileptic medicines. Time required to administer this ACER questionnaire was 15 to 20 min per patient. Patients were not informed of their test scores. Instructions were given prior to start of the test. The Addenbrooke's Cognitive Examination Revised (ACER) Questionnaire is a brief (15–20 min) cognitive test battery designed for dementia screening. It contains 5 sub-scores, each one representing one cognitive domain: attention/concentration (18 points), memory (26 points), fluency (14 points), language (26 points) and visuospatial score (16 points). ACER maximum score is 100, composed by the addition of the all domains.

**Table 1: Addenbrooke's Cognitive Examination Revised (ACER) Questionnaire tests multiple cognitive domains, summed to a score of 100 points 33**

| Cognitive domain | Abilities tested | Score |
|---|---|---|
| Attention and concentration | Orientation, registration, attention and concentration, recall | 18 |
| Memory | Anterograde memory (name and address), retrograde memory, recall (long delay), recognition | 26 |
| Verbal fluency | Letter fluency (p-words), category fluency (animals) | 14 |
| Language | Comprehension, repetition, naming, semantic knowledge | 26 |
| Visuospatial | Copying drawings, drawing a clock face, perception | 16 |

Total 39 or more measurements/patients were needed to have a confidence level of 80% with alpha error of 5 % of the measured value. Addenbrooke's cognitive examination revised [ACER] Questionnaire population reliability value is 0.80.33 Hence we have enrolled 51 patients fulfilling inclusion criteria considering the dropouts.

Statistical Analysis - ACER, age were presented as mean ± SD. Categorical variable (gender) is expressed in actual number & percentage analyzed by Pearson Chi square test. Change in ACER at different time point in two new antiepileptic medicines were analysed by using repeated measures non-parametric ANOVA i.e. Friedman test. As we have three groups with three means, Dunn's Test was used to pinpoint which specific means are significant from the others. Dunn's Multiple Comparison Test is a post hoc (i.e. it's run after an ANOVA). Hence, multiple comparisons were done by Dunn's multiple comparison tests. $P < 0.05$ was considered as statistically significant. Statistical software STATA version 10.0 was used for data analysis.

## 3. Observation and Results

The cognitive functions were assessed in 51 adult patients of both gender having generalized tonic-clonic or partial seizures, out of which 41 completed the study. Age range for the patients was 18-45 years, mean age 29.88 ± 8.33, of which 24 were men and 17 women.

41 patients were treated with newer AEDs Lamotrigine and Zonisamide. The patients were seizure free for the past one year and their mean duration of treatment was 5 years.

**Table 2: Average maintenance dose of antiepileptic medicines**

| Antiepileptic | Average dose (mg/day) |
|---|---|
| T. Lamotrigine | 150 |
| T. Zonisamide | 250 |

As shown in Table 2, the patients were stabilized on new antiepileptic medicines on the mentioned daily dose. The patients were carefully monitored during the follow up period and the epilepsy was well controlled.

**Table 3: Demographic data**

| Antiepileptic | No. of Patients | Mean Age (Years) | Age range (Years) | Men | Women |
|---|---|---|---|---|---|
| Lamotrigine | 20 | 29.05 ± 8.32 | 18 – 45 | 12 | 8 |
| Zonisamide | 21 | 30.14 ± 8.00 | 18 – 45 | 12 | 9 |
| Total | 41 | 29.88 ± 8.33 | 18 – 45 | 24 | 17 |

Age distribution across the treatment groups was analysed by one way ANOVA which was found to be non-significant ($p = 0.929$). Gender distribution was analysed by Pearson Chi square test and was found to be non-significant ($p = 0.913$).

The cognitive performance of patients was analysed on an intention to treat basis by using Addenbrooke's Cognitive Examination Revised [ACER] Questionnaire. Length of time to first follow up was 3 months and length of time to second follow up was 6 months. The analysis was done within groups only depending on the antiepileptic medicine received by the patients.

The cognitive performance of patients on ACER test was analyzed for within treatment difference for two antiepileptic medicines i.e. Lamotrigine and Zonisamide.

**Table 4: Effect of antiepileptic drugs on cognitive function accessed by Addenbrooke's Cognitive Examination Revised [ACER] Questionnaire**

| Antiepileptic | Mean ACER score at different follow up (100) [Mean ± SD] | | | p – values | | |
|---|---|---|---|---|---|---|
| | Baseline | 1st follow up (3 months) | 2nd follow up (6 months) | Baseline vs 1st follow-up | Baseline vs 2nd follow-up | 1st vs 2nd follow-up |
| **Lamotrigine** | 77.7 ± 6.34 | 80.3 ± 5.12 | 83.45 ± 4.65 | **** | **** | **** |
| **Zonisamide** | 75.38 ± 5.5 | 77.33 ± 4.78 | 79.9 ± 4.38 | **** | **** | **** |

(Scores expressed as mean ± standard deviation out of the total score of 100. Scores were analyzed by Friedman test of repeated measures of ANOVA followed by Dunn's multiple comparisons test. ns- Non-significant, $p<0.05$*, $p<0.0001$****)

Table 4 depicts the change in mean Addenbrooke's Cognitive Examination Revised [ACER] Questionnaire score at the baseline and follow ups. The patients were cognitively compromised from the baseline itself as evident from their mean baseline readings which are markedly low than the total score of 100 (mean decrease 20 to 25). The cognitive functions improved significantly at three months and six months follow up (mean increase 5.12 ± 2.67) in patients receiving newer antiepileptic medicines Lamotrigine and Zonisamide ($p < 0.0001$).

**Table 5: Effect of antiepileptic drugs on cognitive function: Attention / Concentration (subscore of ACER)**

| Antiepileptic | Attention / Concentration (18) [Mean ± SD] | | | p - values | | |
|---|---|---|---|---|---|---|
| | Baseline | 1st follow up (3 months) | 2nd follow up (6 months) | Baseline vs 1st follow – up | Baseline vs 2nd follow- up | 1stvs 2nd follow-up |
| **Lamotrigine** | 13.4 ± 1.67 | 13.85 ± 1.35 | 14.7 ± 1.26 | Ns | **** | ** |
| **Zonisamide** | 12.43 ± 1.4 | 12.67 ± 1.2 | 13.24 ± 1.18 | Ns | ** | ns |

(ACER: Addenbrooke's Cognitive Examination Revised Questionnaire. Scores expressed as mean ± standard deviation. Scores were analyzed by Friedman test of repeated measures of ANOVA followed by Dunn's multiple comparisons test. ns- Non-significant, p<0.05*, p<0.01**, p<0.0001****)

Table 5 showed the change in mean attention / concentration sub-score of the ACER questionnaire. Patients showed improvement in attention / concentration ability. Lamotrigine showed highly significant improvement in scores on both three months ($p < 0.01$) and six months ($p < 0.0001$) follow up. Zonisamide also shows significant improvement in scores on six months follow up ($p < 0.01$).

**Table 6: Effect of antiepileptic drugs on cognitive function: Memory (subscore of ACER)**

| Antiepileptic | Memory (26) [Mean ± SD] | | | p – values | | |
|---|---|---|---|---|---|---|
| | Baseline | 1st follow up (3 months) | 2nd follow up (6 months) | Baseline vs 1st follow up | Baseline vs 2nd follow-up | 1stvs 2nd follow-up |
| **Lamotrigine** | 19.55 ± 1.99 | 20.15 ± 1.81 | 20.9 ± 1.59 | Ns | *** | Ns |
| **Zonisamide** | 18.71 ± 1.23 | 19.52 ± 1.25 | 20.43 ± 1.25 | * | **** | * |

(ACER: Addenbrooke's Cognitive Examination Revised Questionnaire. Scores expressed as mean ± standard deviation. Scores were analyzed by Friedman test of repeated measures of ANOVA followed by Dunn's multiple comparisons test. ns- Non-significant, p<0.05*, p<0.001***, p<0.0001****)

Table 6 enlightens the change in mean memory sub-score of the ACER questionnaire. Lamotrigine showed a significant improvement on six months follow up as compared with baseline ($p < 0.001$). Zonisamide resulted in increased memory sub-score which was significant at the three months follow up itself ($p < 0.05$) and highly significant on six months follow up ($p < 0.0001$).

**Table 7: Effect of antiepileptic drugs on cognitive function: Fluency (subscore of ACER)**

| Antiepileptic | Fluency (14) [Mean ± SD] | | | p - values | | |
|---|---|---|---|---|---|---|
| | Baseline | 1st follow up (3 months) | 2nd follow up (6 months) | Baseline vs 1st follow-up | Baseline vs 2nd follow-up | 1stvs 2nd follow-up |
| **Lamotrigine** | 10.4 ± 1.14 | 10.5 ± 1.0 | 11 ± 1.08 | Ns | * | ns |
| **Zonisamide** | 11 ± 1.27 | 11.19 ± 1.03 | 11.43 ± 0.93 | Ns | ns | ns |

(ACER: Addenbrooke's Cognitive Examination Revised Questionnaire. Scores expressed as mean ± standard deviation. Scores were analysed by Friedman test of repeated measures of ANOVA followed by Dunn's multiple comparisons test. ns- Non-significant, p<0.05*, p<0.01**, p<0.001***)

Table 7 mentioned the change in mean fluency subscore of the ACER questionnaire. Patients on Lamotrigine showed significant improvement in fluency on six months follow up when compared with the baseline ($p < 0.05$). Zonisamide also had some increase in score but it was found to be statistically non-significant.

**Table 8: Effect of antiepileptic drugs on cognitive function: Language (subscore of ACER)**

| Antiepileptic | Language (26) [Mean ± SD] | | | p - values | | |
|---|---|---|---|---|---|---|
| | Baseline | 1st follow up (3 months) | 2nd follow up (6 months) | Baseline vs 1st follow-up | Baseline vs 2nd follow-up | 1stvs 2nd follow-up |
| **Lamotrigine** | 21.6 ± 1.73 | 22.55 ± 1.54 | 22.95 ± 1.47 | * | **** | ns |
| **Zonisamide** | 20.52 ± 1.75 | 21 ± 1.58 | 21.43 ± 1.36 | Ns | ** | ns |

(ACER: Addenbrooke's Cognitive Examination Revised Questionnaire. Scores expressed as mean ± standard deviation. Scores were analyzed by Friedman test of repeated measures of ANOVA followed by Dunn's multiple comparisons test. ns- Non-significant, p<0.05*, p<0.01**, p<0.001***, p<0.0001****)

Table 8 observed the change in mean language subscore of the ACER questionnaire. Patients who were on Lamotrigine showed a significant improvement in scores on three months and six months follow up; the six months follow up increase being highly significant as compared to baseline scores ($p < 0.0001$). Patients on Zonisamide also had statistically significant improvement in scores on six months follow up as compared with the baseline ($p < 0.01$).

**Table 9: Effect of antiepileptic drugs on cognitive function: Visuospatial (subscore of ACER)**

| Antiepileptic | Visuospatial (16) [Mean ± SD] | | | p - values | | |
|---|---|---|---|---|---|---|
| | Baseline | 1st follow up (3 months) | 2nd follow up (6 months) | Baseline vs 1st follow-up | Baseline vs 2nd follow-up | 1st vs 2nd follow-up |
| **Lamotrigine** | 12.75 ± 1.41 | 13.25 ± 1.02 | 13.9 ± 0.91 | Ns | **** | * |
| **Zonisamide** | 12.71 ± 1.35 | 12.95 ± 1.24 | 13.38 ± 1.07 | Ns | ** | ns |

(ACER: Addenbrooke's Cognitive Examination Revised Questionnaire. Scores expressed as mean ± standard deviation. Scores were analyzed by Friedman test of repeated measures of ANOVA followed by Dunn's multiple comparisons test. ns- Non-significant, p<0.05*, p<0.01**, p<0.0001****)

Table 9 showed the change in mean visuospatial subscore of the ACER questionnaire. Patients receiving Lamotrigine showed highly significant improvement in visuospatial skills on six months follow up when compared with baseline ($p< 0.0001$). Patients receiving Zonisamide also showed significant improvement in scores at six months follow up ($p < 0.01$).

## 4. Discussion

Cognitive side effects of anti-epileptic medicines are the major dose related limiting factors during the therapy of epilepsy. Cognitive impairments have definite implications on likelihood of adherence to chronic treatment. The present study was framed to evaluate the progress of cognitive effects to newer (Lamotrigine and Zonisamide) AEDs. It was a prospective observational cohort study comprising of 41 adult patients of both gender having generalized tonic-clonic or partial seizures and on newer antiepileptic medicine as monotherapy with a seizure free period of one year.

Standardized tests of objective assessment of cognition i.e. Addenbrooke's Cognitive Examination Revised [ACER] Questionnaire was used. Patients were evaluated three times, baseline i.e. at the time of enrolment, 3 months of follow up and six months of follow up.

The basic demographic data of the sample was comparable for age and gender distribution. The primary finding of the present study is that there was a marked improvement in the cognitive performance of patients receiving newer AEDs (Lamotrigine and Zonisamide) on attention, concentration, memory, verbal fluency, language and visuospatial skills.

Results of Addenbrooke's Cognitive Examination Revised [ACER] Questionnaire - After complete follow up, there was significant improvement of cognitive performance in patients receiving newer AEDs Lamotrigine and Zonisamide. Ijff *et al* in their meta-analysis got similar results where traditional, older antiepileptic agents showed deleterious effects on cognition [7]. For Lamotrigine, there is evidence of a cognition enhancing effect and for Zonisamide the data was limited. Cavanna *et al* in their review found that older antiepileptic medicines acting through GABA are noted to have sedating and cognitive slowing effects [8]. Lamotrigine has shown efficacy in alleviating affective symptoms in patients with epilepsy. Zonisamide was frequently associated with mild sleepiness and sedation and is only rarely implicated in severe cognitive side-effects.

Attention / concentration subscore of ACER questionnaire - The scores had statistically improved in patients on Zonisamide and were highly significant in patients on Lamotrigine. Glauser *et al* in their double blind, randomized trial comparing ethosuximide, sodium valproate and Lamotrigine, found that patients on sodium valproate experienced a higher rate of adverse events leading to drug discontinuation as well as significant negative effects on attentional measures [9]. Ijff *et al* in their meta-analysis found that Lamotrigine has enhancing effect on attention ability as compared with older AEDs [7]. Eun *et al* in their randomized, multicentre trial found that Zonisamide in lower doses (3-4 mg/kg/day) had similar efficacy and more beneficial neurocognitive effects compared to higher doses (6-8 mg/kg/day) [10]. This finding is in accordance with the present study where patients were stabilized on an average dose of 250 mg/day.

Memory subscore of ACER questionnaire - As seen with overall ACER questionnaire score, memory deficits showed significant improvement in patients receiving newer AEDs Lamotrigine and Zonisamide. Pavuluri *et al* found that Lamotrigine treatment significantly improved working and verbal memory as compared to healthy controls [11]. Berent *et al* reported that there was evidence of cognitive side effects with use of Zonisamide. However, there was development of tolerance to these adverse effects [12]. This phenomenon may be responsible for the beneficial effects seen in this study as the patients were stabilized on Zonisamide monotherapy for more than one year.

Verbal fluency subscore of ACER questionnaire - Lamotrigine therapy had resulted in increased verbal fluency. Daban *et al* in their comparative study found that Lamotrigine treated patients had better performance in verbal fluency task and immediate verbal memory test (California Verbal Learning Test) than the patients receiving carbamazepine or sodium valproate [13].

Language subscore of ACER questionnaire - Lamotrigine and Zonisamide had significant beneficial effects on language skills. Meador *et al* in their multicentric, prospective observational study found that sodium valproate and carbamazepine therapy is correlated with dose dependent decrease in verbal and non-verbal abilities evaluated by Differential Ability Scales, Preschool Language Scale, Peabody Picture Vocabulary Test and Developmental Test of Visual-Motor Integration [14]. No dose effects were seen for Lamotrigine and phenytoin. Makatsori *et al* in a double blind, placebo controlled study found that Lamotrigine therapy resulted in better performance on public speech which was correlated to stimulatory role of glutamate [15].

Eun *et al* found that problems with language and vocabulary are evident in patients receiving high dose (6-8 mg/kg/day) of Zonisamide; while such effects are not present when Zonisamide is administered in low dose (3-4 mg/kg/day) [10]. Visuospatial skills subscore of ACER questionnaire - In the present study, visuospatial skills improvement was seen in Lamotrigine and Zonisamide treated patients. Mills *et al* in a randomized, double-blind study evaluated visuomotor skills through Performance On-Line (POL) testing. Lamotrigine group showed no detrimental effects [16].

Studies evaluating the effect of Zonisamide on visuospatial skills are lacking. The beneficial effects found in the current study may be related to long term maintenance of patients on low dose therapy.

## 5. Conclusion

Several studies have examined the established old AEDs but no certain conclusions have been reached as to what degree individual drugs have an effect on cognition. Data regarding the cognitive effects of the new drugs are sparse. In our study, Newer AEDs Lamotrigine and Zonisamide had shown positive outcome on the cognitive performance for the parameters of attention, concentration, memory, verbal fluency, language and visuospatial skills. Our research can further proceed with conducting the comparative study between cognitive effects of older versus newer antiepileptic drugs to prove the new drugs superiority for maintaining cognitive function.

**Acknowledgement**

We would like to acknowledge the clinical and supporting staff of department of medicine and psychiatry including post graduate students.

**Conflict of interest**

The authors report no conflicts of interest in this work.

## References

[1]. Joseph I. Sirven. Epilepsy: A Spectrum Disorder. *Cold Spring Harb Perspect Med* 2015: a022848.

[2]. Carl E. Stafstrom and Lionel Carmant. Seizures and Epilepsy: An Overview. *Cold Spring Harb Perspect Med* 2015: a022426.

[3]. Eddy CM, Rickards HE, Cavanna AE. Behavioral adverse effects of antiepileptic drugs in epilepsy. *J Clin Psychopharmacol.* 2012; 32 (3):362-75.

[4]. Eddy CM, Rickards HE, Cavanna AE. The cognitive impact of antiepileptic drugs. *Ther Adv Neurol Disord.* 2011; 4(6):385-407.

[5]. French JA, Staley BA. AED Treatment Through Different Ages: As Our Brains Change, Should Our Drug Choices Also? *Epilepsy Curr.* 2012; 12(Suppl 3):22-7.

[6]. Cramer JA, Mintzer S, Wheless J, Mattson RH. Adverse effects of antiepileptic drugs: a brief overview of important issues. *Expert Rev Neurother*. 2010; 10(6):885-91.

[7]. Ijff DM, Aldenkamp AP. Cognitive side-effects of antiepileptic drugs in children. *Handb Clin Neurol.* 2013; 111:707-18.

[8]. Cavanna AE, Ali F, Rickards HE, McCorry D. Behavioral and cognitive effects of anti-epileptic drugs. *Discov Med.* 2010; 9(45):138-44.

[9]. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, Clark PO, Adamson PC; Childhood Absence Epilepsy Study Team. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. *Epilepsia.* 2013; 54(1): 141-55.

[10]. Eun SH, Kim HD, Eun BL, Lee IK, Chung HJ, Kim JS, Kang HC, Lee YM, Suh ES, Kim DW, Eom S, Lee JS, Moon HK. Comparative trial of low- and high-dose Zonisamide as monotherapy for childhood epilepsy. *Seizure*. 2011; 20(7): 558-63.

[11]. Pavuluri MN, Passarotti AM, Mohammed T, Carbray JA, Sweeney JA. Enhanced working and verbal memory after Lamotrigine treatment in pediatric bipolar disorder. *Bipolar Disord.* 2010; 12(2): 213–220.

[12]. Berent S, Sackellares JC, Giordani B, Wagner JG, Donofrio PD, Abou-Khalil B. Zonisamide (CI-912) and cognition: results from preliminary study. *Epilepsia.* 1987; 28(1):61-7.

[13]. Daban C, Martínez-Arán A, Torrent C, Sánchez-Moreno J, Goikolea JM, Benabarre A, Comes M, Colom F, Vieta E. Cognitive functioning in bipolar patients receiving Lamotrigine: preliminary results. *J Clin Psychopharmacol.* 2006; 26(2): 178-81.

[14]. Meador KJ, Baker GA, Browning N, Cohen MJ, Clayton-Smith J, Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Foetal antiepileptic drug exposure and verbal versus non-verbal abilities at three years of age. *Brain.* 2011; 134(Pt 2): 396-404.

[15]. Makatsori A, Duncko R, Moncek F, Loder I, Katina S, Jezova D. Modulation of neuroendocrine response and non-verbal behavior during psychosocial stress in healthy volunteers by the glutamate release-inhibiting drug Lamotrigine. *Neuroendocrinology.* 2004; 79(1): 34-42.

[16]. Mills KC, Drazkowski JF, Hammer AE, Caldwell PT, Kustra RP, Blum DE. Relative influences of adjunctive topiramate and adjunctive Lamotrigine on scanning and the effective field of view. *Epilepsy Res.* 2008; 78(2-3):140-6. Epub 2007 Dec 21. *Erratum in: Epilepsy Res*. 2009; 86(1):99.