

The effect of levetiracetam on depression and anti-oxidant activity in patients with epilepsy

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Keywords

Epilepsy; Depression; Zinc; Glutathione; Oxidative Stress

Abstract

Background: Levetiracetam (LEV) is approved for treating epilepsy. The current evidence shows that LEV can cause behavioral problems such as depression. It is well-known that depression is associated with oxidative stress. Therefore, we conducted this study to assess the influence of LEV on depression severity and anti-oxidant status.

Methods: In this prospective longitudinal study, 50 patients with diagnosis of epilepsy on LEV were included. We used Beck Depression Inventory-II (BDI-II) to assess depression severity. The serum levels of zinc and glutathione were measured as anti-oxidant markers. These variables were evaluated at the baseline and 3 months after the commencement of LEV.

Results: A total of 30 patients finished the follow-up. Among them, 21 patients were women. The mean age at baseline was 28.76 ± 11.37 (range: 16-68 years). The severity of depression at the last follow-up was significantly higher than the baseline. We observed a

decrease in the serum levels of zinc and glutathione, though they were not statistically significant.

Conclusion: Our results suggest that LEV can increase the risk of depression in patients with epilepsy. This study also suggests that zinc depletion can be induced through act of LEV. Further studies are needed to validate these findings.

Introduction

Until 1990, there were limited anti-seizure medications. Since then, several anti-seizure medications have been developed and introduced. Levetiracetam (LEV), the S-enantiomer of alpha-ethyl-2-oxo-1-pyrrolidine acetamide, was initially approved for treatment of focal seizure.¹ The clinical effectiveness of LEV in generalized seizures has been reported in prior clinical trials.²⁻⁴

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LEV is safe and relatively well tolerated in most cases. Behavioral safety of LEV has received much attention in the past decade. The rate of behavioral and mood problems in epileptic patients with LEV have been reported in a range from 0.3% to 13.5%, depending on the study design and assessing methods.^{5,6} It is not clear how LEV can lead to depression. Studies suggest that anti-seizure medications are associated with oxidative stress resulting in developing behavioral, mood, and cognition dysfunctions.^{7,8}

A growing body of literature has investigated the effect of LEV on oxidative stress. It is commonly believed that LEV augments oxidative stress, but the evidence is mixed. Some studies reported that LEV could decrease antioxidant activities.⁸⁻¹⁰ In contrast, others showed a protection effect of LEV against oxidative stress in animal models.^{11,12} On the other hand, some studies showed no effect of these agents on oxidative stress activity.^{13,14}

Glutathione is the most abundant thiol compound in animal cells and the most important intracellular antioxidant.^{15,16} This has different roles in the pathogenesis of a wide range of diseases such as diabetes mellitus, Parkinson's disease, and multiple sclerosis.^{17,18} Zinc has been known as one of the most effective minerals in antioxidants.¹⁹ There is evidence regarding the association between behavioral alteration and depressive disorders with oxidative stress.²⁰ It is well-known that alteration in glutathione level has an important role in pathophysiology of psychological disorders including major depression disorder, bipolar disorder, and schizophrenia.^{21,22} The effect of reduced zinc on developing and pathophysiology of depressions has been reported in several studies.^{23,24}

In the current study, we examined two hypotheses. First, LEV would be associated with depression. Therefore, we evaluated depression score through Beck Depression Inventory-II (BDI-II) questionnaire before and three months after the commencement of LEV. Second, LEV could influence antioxidant activity. Therefore, we measured the serum level of glutathione and zinc as antioxidant markers before and 3 months after LEV oral treatment.

Materials and Methods

Study population: This study was conducted in Kashani Comprehensive Epilepsy Center, affiliated to Isfahan University of Medical

Sciences, Isfahan, Iran, from March 2018 to December 2019. Patients with diagnosis of epilepsy who had planned to receive LEV therapy were included. Patients who had abnormal neurological examination, abnormal magnetic resonance imaging (MRI) finding, other neurological disorders, and a history of disease which might affect antioxidant enzymes were excluded from the study. This study was approved by the regional bioethics committee of Isfahan University of Medical Sciences and in all cases, patients' written informed consent was obtained.

Procedure: In this prospective study, we assessed definite patients with epilepsy who were supposed to start LEV with dose of 1000-3000 mg/day. LEV was started for patients with decision of a trained neurologist with specialty in epilepsy (JMH). We performed two assessments at the baseline (date of starting LEV therapy) and 3 months after the commencement of LEV. At the baseline, detailed demographic and clinical characteristics including age, sex, age at diagnosis, comorbidities, and drug history were obtained. All patients also underwent a comprehensive assessment. Neurological examination was conducted for evaluation of neurological status. Electroencephalography (EEG) was done using the international 10-20 system including T1 and T2 electrodes on all patients. MRI was conducted on all patients.

Questionnaire: To assess depression, we used the Iranian version of BDI-II.²⁵ The BDI-II appraises a range of depression symptoms including sadness, pessimism, sense of failure, loss of pleasure, guilt, punishment, self-dislike, self-criticalness, suicidal thoughts, crying, agitation, irritability, social withdrawal, indecisiveness, worthlessness, loss of energy, change in sleep pattern, change in appetite, loss of concentration, fatigability, and loss of libido. This scale consists of 21 items and respondents are asked to rate these items on a 4-point scale (0-3). The global BDI-II score range was from 0 to 63, with higher score indicating more severe depression.²⁶ The questionnaire was completed at baseline and at the end of follow-up.

Measurements: To assess antioxidant activity, we measured the serum levels of glutathione and zinc. A sample of 5 cc venous blood was collected. Zinc was assessed using colorimetric assay kit [based on the 5-Br-3'-phosphoadenosine-5'-phosphosulfate (5-Br-PAPS)]. In this method, zinc measurement is based on the reaction of zinc with

specific complexant 5-Br-PAPS form at pH = 8.6, in a buffer media. The serum level of glutathione was detected spectrophotometrically by monitoring the reaction of glutathione with 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB). The serum levels of glutathione and zinc were measured at the baseline and the end of follow-up.

Descriptive data were presented as mean ± standard deviation (SD) or frequency (%) for interval and categorical variables, respectively. The one-sample Kolmogorov-Smirnov test was performed for checking the normality of variables. We carried out dependent t-test to assess change in variables following treatment. Pearson's correlations test was performed to assess correlation of depression score with the zinc and glutathione levels. We conducted all statistical analyses using SPSS software (version 22, IBM Corporation, Armonk, NY, USA) and a P-value less than 0.05 was considered as significant.

Results

We approached 50 patients, 10 refused to participate and 6 were excluded (due to other neurological or inflammatory disorders). Besides, 4 patients did not complete the follow-up. The complete cohort of patients included 30 patients (Figure 1).

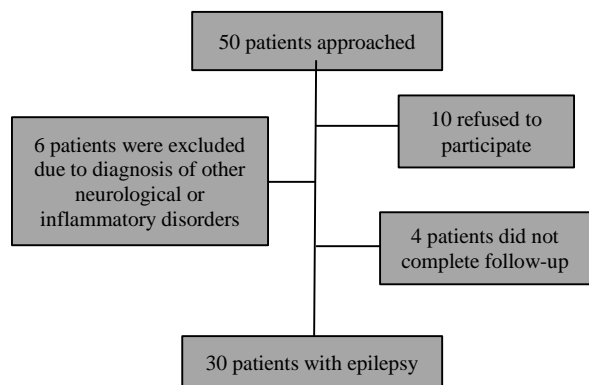


Figure 1. The study flowchart

Among included patients, 21 were women (70.0%). The mean age at epilepsy onset was

15.89 ± 11.67 years (range: 3 to 47 years) and the mean age at baseline was 28.76 ± 11.37 (range: 16 to 68 years). These findings and clinical characteristics of patients are presented in table 1.

Table 1. Demographic and clinical characteristics

Variable	Patients (n = 30)
Age at onset (year) (mean ± SD)	15.89 ± 11.67
Age at baseline (year) (mean ± SD)	28.76 ± 11.37
Gender	
Women	21 (70.0)
Men	9 (30.0)
Seizure type	
Generalized	21 (70.0)
Focal	9 (30.0)
Seizure frequency	
Daily	0 (0)
Weekly	1 (3.3)
Monthly	17 (56.7)
Annual	10 (33.3)
Less than once a year	2 (6.7)
EEG [n (%)]	
Abnormal	11 (36.7)
Normal	19 (63.3)

EEG: Electroencephalography; SD: Standard deviation

As table 2 shows, the mean glutathione serum level at follow-up visit was lower than the baseline (P < 0.001). Although there was a decrease in glutathione level, the difference was not statistically significant (P = 0.068). The mean of zinc concentration decreased significantly (P < 0.001). The mean of BDI-II score at follow-up visit was higher than baseline (P < 0.001).

To evaluate the possible role of gender, we analyzed the change of variables separated by gender. Female patients had a significant increase in BDI-II score (P < 0.001). Moreover, female patients had lower glutathione levels at the end of follow-up compared to the baseline (P = 0.007). No significant change in zinc levels was found in female patients (P = 0.836). Similarly, there was no statistically significant change in zinc and glutathione serum levels in male patients (P = 0.133 and P = 0.823, respectively). But, BDI-II score increased significantly (P = 0.023). The information is documented in table 3.

There was no significant correlation between BDI-II score, zinc and glutathione levels at the baseline and at the end of follow-up (Table 4).

Table 2. Change of depression, serum level of glutathione and zinc from baseline to the end of follow-up

	Baseline	End of follow-up	Mean difference	95% CI	t (29)	P
BDI-II	8.60 ± 6.60	13.73 ± 7.40	5.13 ± 4.28	-6.73, -3.53	-6.55	< 0.001
Glutathione serum level (µg/do)	381.60 ± 135.19	349.35 ± 159.77	-66.78 ± 166.72	-5.31, 138.88	1.92	0.068
Zinc serum level (µg/do)	80.08 ± 18.33	73.46 ± 18.88	-6.68 ± 14.11	0.42, 12.93	2.22	< 0.001

Data are presented as mean ± standard deviation (SD)

CI: Confidence interval; BDI-II: Beck Depression Inventory-II

Table 3. Change of depression, serum level of glutathione and zinc from baseline to follow-up visit separated by gender

		Baseline	End of follow-up	Mean difference	95% CI	t	P
BDI-II	Women	9.28 ± 7.19	15.33 ± 6.77	-6.04 ± 4.43	-8.06, -4.02	-6.252	< 0.001
	Men	7.00 ± 4.94	10.00 ± 7.87	-3.00 ± 3.20	-5.46, -0.53	-2.811	0.023
Glutathione (µg/do)	Women	386.94 ± 136.50	288.70 ± 120.16	98.23 ± 131.61	30.56, 165.90	3.077	0.007
	Men	402.83 ± 150.02	425.16 ± 230.40	-22.33 ± 323.35	-266.17, 221.50	-0.235	0.823
Zinc (µg/do)	Women	76.56 ± 19.26	72.18 ± 20.46	-1.35 ± 26.53	-14.99, 12.28	-0.210	0.836
	Men	86.33 ± 11.91	73.50 ± 21.57	4.37 ± 12.48	-2.27, 11.02	1.402	0.181

Data are presented as mean ± standard deviation (SD)

CI: Confidence interval; BDI-II: Beck Depression Inventory-II

Table 4. Correlation between Beck Depression Inventory-II (BDI-II) score, zinc and glutathione levels at the baseline and end of follow-up

	BDI-II	r correlation	
		Zinc	Glutathione
At baseline			
BDI-II	1.000	0.070 (0.747)	-0.155 (0.456)
Zinc	-	1.000	-0.301 (0.153)
At end of follow-up			
BDI-II	1.000	0.263 (0.176)	-0.182 (0.353)
Zinc	-	1.000	-0.167 (0.395)

BDI-II: Beck Depression Inventory-II

Discussion

One of the most important adverse effects of LEV is behavioral disorder such as depression. In the current study, we assessed depression and anti-oxidant levels in patients with epilepsy who received LEV. Our results showed an important increase in depression score, but a non-significant decrease in zinc and glutathione.

With the first hypothesis, we assumed that LEV would be associated with depression, and the data showed a significant increase in depression scores three months after the commencement of LEV. Our result is in agreement with previous studies showing increased rate of depression in patients who were on LEV.^{27,28} Neurobiological evidence indicates the association between LEV and sodium valproate.²⁹ On the other hand, some studies have shown the relation of this receptor with depression.^{30,31} Our outcome is contrary to that of Mazza *et al.* who found that treatment with LEV could improve depression and anxiety in patients with focal seizure.³² A possible explanation for this finding might be that improvement in depression and anxiety was caused by improvement in seizure frequency, not due to LEV psychotropic effect. However, they did not

report depression score with respect to the frequency of seizures. Our results are also in disagreement with Hagemann *et al.* However, they found no improvement in depression and anxiety in patients who were converted to LEV monotherapy. In addition, eight (5.7%) patients discontinued LEV for psychiatric adverse effect.³³ This inconsistency between studies may be due to differences in phenomenon of epilepsy, duration of study, past history of other medications, and instrument which was used to measure depression.

Other factors such as release phenomenon, drug interaction, and alternative or reciprocal psychosis have been suggested to influence behavioral status in patients with epilepsy. The release phenomenon occurs in patients with epilepsy who have been disabled intellectually, who become more able to misbehave result in the improvement of seizure control. In the current study, no patients had been disabled intellectually and physically before the beginning of study. No patients used other medications six months before and within the study. We also assessed psychosis symptoms in patients and no one reported psychosis before and during the study.

With respect to the second research hypothesis, we found no significant change in glutathione concentration. Unexpectedly, we found a decrease in zinc levels. This result can be related to small sample size and short follow-up duration in our sample. Zinc depletion was observed in patients with epilepsy who underwent antiepileptic drugs (AEDs), particularly valproic acid.³⁴ It has been suggested that impairment in zinc absorption and zinc chelation can lead to reducing zinc bioavailability.³⁴ However, there are little published data on the effect of LEV on trace elements such as zinc. Sarangi *et al.* found a higher zinc concentration in patients on LEV, valproic acid, carbamazepine, phenytoin, and lamotrigine compared to healthy group.³⁵ The

main weakness in their study is cross-sectional design. In agreement with our study, two case report studies presented patients who had undergone LEV therapy and had hair loss due to zinc deficiency.^{36,37} Taken together, our study was unable to find an anti-oxidative effect of LEV.

It is now well established from a variety of studies that imbalance between the glutamatergic and gamma-aminobutyric acid (GABA) ergic systems can cause depression. It has been suggested that zinc deficiency or its impaired function can induce depression via its effect on glutamatergic and GABAergic receptors.³⁸ Previous studies showed that LEV negatively affected zinc function by inhabitation of the zinc antagonism on GABAergic and glycine receptors.³⁹ In the current study, we did not find a relation between depression score and zinc levels at the baseline and at the end of follow-up.

Up to now, several studies have shown that zinc deficiency can cause oxidative stress.^{40,41} N-methyl-D-aspartate (NMDA) receptors - ionotropic glutamate receptors - are modulated by trace elements such as zinc. Zinc deficiency promotes the activity of NMDA receptor resulting in activation of leukocytes and macrophages. Besides, this can induce the production of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and nitric oxide.⁴⁰ As mentioned above, the interaction between LEV and zinc can affect glutamatergic and GABAergic receptors such as NMDA receptor. Thus, it can be suggested that LEV may reduce oxidative activity through its effect on association between zinc activities and glutamatergic and GABAergic receptors.

A decreased level of glutathione in patients with epilepsy has previously been observed.^{42,43}

References

1. Sills GJ, Rogawski MA. Mechanisms of action of currently used antiepileptic drugs. *Neuropharmacology* 2020; 168: 107966.
2. Manreza MLG, Pan TA, Carbone EQ, Vattimo ACA, Herrera R, Morais DC, et al. Efficacy and safety of levetiracetam as adjunctive therapy for refractory focal epilepsy. *Arq Neuropsiquiatr* 2021; 79(4): 290-8.
3. Marson A, Burnside G, Appleton R, Smith D, Leach JP, Sills G, et al. The SANAD II study of the effectiveness and cost-effectiveness of levetiracetam, zonisamide, or lamotrigine for newly diagnosed focal epilepsy: An open-label, non-inferiority, multicentre, phase 4, randomised controlled trial. *Lancet* 2021; 397(10282): 1363-74.
4. Lee SK, Lee SA, Kim DW, Loesch C, Pelgrims B, Osakabe T, et al. A randomized, open-label, multicenter comparative trial of levetiracetam and topiramate as adjunctive treatment for patients with focal epilepsy in Korea. *Epilepsy Behav* 2019; 97: 67-74.
5. Steinhoff BJ, Klein P, Klitgaard H, Laloyaux C, Moseley BD, Ricchetti-Masterson K, et al. Behavioral adverse events with brivaracetam, levetiracetam, perampanel, and topiramate: A systematic review. *Epilepsy Behav* 2021; 118: 107939.
6. Chung S, Williams B, Dobrinsky C, Patten A, Yang H, Laurenza A. Perampanel with concomitant levetiracetam and topiramate: Post hoc analysis of adverse events related to hostility and aggression. *Epilepsy Behav* 2017; 75: 79-85.
7. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. *BMJ* 2014; 348: g254.
8. Varoglu AO, Yildirim A, Aygul R, Gundogdu OL, Sahin YN. Effects of valproate, carbamazepine, and levetiracetam on the antioxidant and oxidant systems in epileptic patients and their clinical importance. *Clin Neuropharmacol* 2010; 33(3): 155-7.
9. Sarangi SC, Kakkar AK, Kumar R, Gupta YK. Effect of lamotrigine, levetiracetam & topiramate on neurobehavioural parameters & oxidative stress in comparison with valproate in rats. *Indian J Med Res* 2016; 144(1): 104-11.
10. Baysal M, Ilgin S, Kilic G, Kilic V, Ucarcan S, Atli O. Reproductive toxicity after levetiracetam administration in male rats: Evidence for role of hormonal status

Some studies on animal models suggested that LEV might prevent the loss of glutathione in the hippocampal region.^{44,45} In contrast to these studies, Menon et al. found no relation between LEV and glutathione concentration.⁴⁶ In the present study, we found a substantial decrease in the glutathione concentration among female patients, but not male patients.

Our study has several limitations. The most important limitation is the study design. A randomized controlled trial study is needed to assess the effect of LEV on oxidative activity in patients with epilepsy. Another limitation is small sample size. Our study is also limited by short follow-up duration. We used questionnaire to assess depression, which is not a gold standard to evaluate psychological diseases.

Conclusion

This longitudinal study suggests that LEV therapy may induce depression. However, this finding may be specific to patients with epilepsy; thus, no conclusion regarding other diseases, especially psychological disorders, can be drawn. We also found reduction in the zinc levels in our patients. Further studies are needed to validate these findings.

Conflict of Interests

The authors declare no conflict of interest in this study.

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- and oxidative stress. *PLoS One* 2017; 12(4): e0175990.
11. de Albuquerque Oliveira A, Linhares MI, Filho AJ MC, Rios ERV, de Carvalho Lima CN, Venancio ET, et al. Antioxidant properties of antiepileptic drugs levetiracetam and clonazepam in mice brain after in vitro-induced oxidative stress. *Afr J Pharm Pharmacol* 2016; 10(14): 278-88.
 12. Ueda Y, Doi T, Takaki M, Nagatomo K, Nakajima A, Willmore LJ. Levetiracetam enhances endogenous antioxidant in the hippocampus of rats: In vivo evaluation by brain microdialysis combined with ESR spectroscopy. *Brain Res* 2009; 1266: 1-7.
 13. Mahdavi A, Naeini AA, Najafi M, Maracy M, Ghazvini MA. Effect of levetiracetam drug on antioxidant and liver enzymes in epileptic patients: Case-control study. *Afr Health Sci* 2020; 20(2): 984-90.
 14. Morimoto M, Satomura S, Hashimoto T, Kyotani S. A study of oxidative stress and the newer antiepileptic drugs in epilepsy associated with severe motor and intellectual disabilities. *J Chin Med Assoc* 2017; 80(1): 19-28.
 15. Forman HJ, Zhang H, Rinna A. Glutathione: Overview of its protective roles, measurement, and biosynthesis. *Mol Aspects Med* 2009; 30(1-2): 1-12.
 16. Gaucher C, Boudier A, Bonetti J, Clarot I, Leroy P, Parent M. Glutathione: Antioxidant properties dedicated to nanotechnologies. *Antioxidants (Basel)* 2018; 7(5): 62.
 17. Kung HC, Lin KJ, Kung CT, Lin TK. Oxidative stress, mitochondrial dysfunction, and neuroprotection of polyphenols with respect to resveratrol in Parkinson's disease. *Biomedicines* 2021; 9(8): 918.
 18. Olla S, Steri M, Formato A, Whalen MB, Corbisiero S, Agresti C. Combining human genetics of multiple sclerosis with oxidative stress phenotype for drug repositioning. *Pharmaceutics* 2021; 13(12): 2064.
 19. El-Bahr SM, Shousha S, Albokhadaim I, Shehab A, Khattab W, Ahmed-Farid O, et al. Impact of dietary zinc oxide nanoparticles on selected serum biomarkers, lipid peroxidation and tissue gene expression of antioxidant enzymes and cytokines in Japanese quail. *BMC Vet Res* 2020; 16(1): 349.
 20. Barbosa ML, de Meneses AAPM, de Aguiar RPS, de Castro e Sousa JM, de Carvalho Melo Cavalcante AA, Maluf SW. Oxidative stress, antioxidant defense and depressive disorders: A systematic review of biochemical and molecular markers. *Neurology, Psychiatry and Brain Research* 2020; 36: 65-72.
 21. Nucifora LG, Tanaka T, Hayes LN, Kim M, Lee BJ, Matsuda T, et al. Reduction of plasma glutathione in psychosis associated with schizophrenia and bipolar disorder in translational psychiatry. *Transl Psychiatry* 2017; 7(8): e1215.
 22. Zalachoras I, Hollis F, Ramos-Fernandez E, Trovo L, Sonnay S, Geiser E, et al. Therapeutic potential of glutathione-enhancers in stress-related psychopathologies. *Neurosci Biobehav Rev* 2020; 114: 134-55.
 23. Yosae S, Clark CCT, Keshtkaran Z, Ashourpour M, Keshani P, Soltani S. Zinc in depression: From development to treatment: A comparative/ dose response meta-analysis of observational studies and randomized controlled trials. *Gen Hosp Psychiatry* 2022; 74: 110-7.
 24. da Silva LEM, de Santana MLP, Costa PRF, Pereira EM, Nepomuceno CMM, Queiroz VAO, et al. Zinc supplementation combined with antidepressant drugs for treatment of patients with depression: A systematic review and meta-analysis. *Nutr Rev* 2021; 79(1): 1-12.
 25. Ghassemzadeh H, Mojtabai R, Karamghadiri N, Ebrahimkhani N. Psychometric properties of a Persian-language version of the Beck Depression Inventory--Second edition: BDI-II-PERSIAN. *Depress Anxiety* 2005; 21(4): 185-92.
 26. Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. *J Pers Assess* 1996; 67(3): 588-97.
 27. Mula M, Trimble MR, Yuen A, Liu RS, Sander JW. Psychiatric adverse events during levetiracetam therapy. *Neurology* 2003; 61(5): 704-6.
 28. White JR, Walczak TS, Leppik IE, Rarick J, Tran T, Beniak TE, et al. Discontinuation of levetiracetam because of behavioral side effects: A case-control study. *Neurology* 2003; 61(9): 1218-21.
 29. Helmstaedter C, Mihov Y, Toliat MR, Thiele H, Nuernberg P, Schoch S, et al. Genetic variation in dopaminergic activity is associated with the risk for psychiatric side effects of levetiracetam. *Epilepsia* 2013; 54(1): 36-44.
 30. Taylor WD, Zald DH, Felger JC, Christman S, Claassen DO, Horga G, et al. Influences of dopaminergic system dysfunction on late-life depression. *Mol Psychiatry* 2022; 27(1): 180-91.
 31. Hasbi A, Nguyen T, Rahal H, Manduca JD, Miksys S, Tyndale RF, et al. Sex difference in dopamine D1-D2 receptor complex expression and signaling affects depression- and anxiety-like behaviors. *Biol Sex Differ* 2020; 11(1): 8.
 32. Mazza M, Martini A, Scopetta M, Mazza S. Effect of levetiracetam on depression and anxiety in adult epileptic patients. *Prog Neuropsychopharmacol Biol Psychiatry* 2008; 32(2): 539-43.
 33. Hagemann A, May TW, Nieder E, Witte Bolt K, Pohlmann-Eden B, Elger CE, et al. Quality of life, anxiety and depression in adult patients after add-on of levetiracetam and conversion to levetiracetam monotherapy. *Epilepsy Res* 2013; 104(1-2): 140-50.
 34. Castro-Gago M, Perez-Gay L, Gomez-Lado C, Castineiras-Ramos DE, Otero-Martinez S, Rodriguez-Segade S. The influence of valproic acid and carbamazepine treatment on serum biotin and zinc levels and on biotinidase activity. *J Child Neurol* 2011; 26(12): 1522-4.
 35. Sarangi SC, Tripathi M, Kakkar AK, Gupta YK. Effect of antiepileptic therapy on trace elements status in Indian population in a tertiary care hospital from northern India: a cross sectional study. *Epilepsy Res* 2014; 108(5): 917-27.
 36. Vajihah A, Zahra GK, Andisheh M, Padideh G. Role of zinc supplementation in the treatment of levetiracetam-induced hair loss: A case series. *J Pharm Care* 2017; 4(1-2): 44-5.
 37. Zou X, Hong Z, Zhou D. Hair loss with levetiracetam in five patients with epilepsy. *Seizure* 2014; 23(2): 158-60.
 38. Mlyniec K. Zinc in the Glutamatergic Theory of Depression. *Curr Neuropharmacol* 2015; 13(4): 505-13.
 39. Palm R, Hallmans G. Zinc and copper metabolism in phenytoin therapy. *Epilepsia* 1982; 23(5): 453-61.
 40. Marreiro DD, Cruz KJ, Morais JB, Beserra JB, Severo JS, de Oliveira AR. Zinc and Oxidative Stress: Current Mechanisms. *Antioxidants (Basel)* 2017; 6(2): 24.
 41. Prasad AS. Zinc is an antioxidant and anti-inflammatory agent: Its role in human health. *Front Nutr* 2014; 1: 14.
 42. Mueller SG, Trabesinger AH, Boesiger P, Wieser HG. Brain glutathione levels in patients with epilepsy measured by in vivo (1)H-MRS. *Neurology* 2001; 57(8): 1422-7.
 43. Wang M, Zhang X, Jia W, Zhang C, Boczek T, Harding M, et al. Circulating glutathione peroxidase and superoxide dismutase levels in patients with epilepsy: A meta-analysis. *Seizure* 2021; 91: 278-86.
 44. Gibbs JE, Walker MC, Cock HR. Levetiracetam: antiepileptic properties and protective effects on mitochondrial dysfunction in experimental status epilepticus. *Epilepsia* 2006; 47(3): 469-78.
 45. Oliveira AA, Almeida JP, Freitas RM, Nascimento VS, Aguiar LM, Junior HV, et al. Effects of levetiracetam in lipid peroxidation level, nitrite-nitrate formation and antioxidant enzymatic activity in mice brain after pilocarpine-induced seizures. *Cell Mol Neurobiol* 2007; 27(3): 395-406.
 46. Menon B, Ramalingam K, Kumar RV. Low plasma antioxidant status in patients with epilepsy and the role of antiepileptic drugs on oxidative stress. *Ann Indian Acad Neurol* 2014; 17(4): 398-404.