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The efficacy of Vitamin B6 and alpha-lipoic acid in preventing levetiracetam depressant-like behavior in mice

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ABSTRACT

Background: Some antiepileptic drugs for instance levetiracetam cause depression in patients. Vitamin B6 is a cofactor involved in the neurotransmitter synthesis. α-Lipoic acid (ALA) is a mitochondrial cofactor that can prevent neuronal damage. The aim of this study was to evaluate the effectiveness of B6 and ALA for preventing levetiracetam depression in mice. **Methods**: Male NMRI mice (weighing 25 ± 3 g) were used. Levetiracetam (20 mg/kg), and pretreatments with ALA (20, 40 mg/kg), Vitamin B6 (100 mg/kg), or imipramine (10 mg/kg) as the control positive were all administered intraperitonealy for 14 consecutive days. The locomotor test and forced swimming test (FST) were performed on days 7 and 15 on same groups of animals, novelty suppressed feeding test (NSFT) was tested on day 16. **Results**: Immobility time in FST increased following levetiracetam administration (day 7, 166 ± 5.63s vs. control 135 ± 9.9s, $P = 0.020$; day15, 188 ± 6.45s vs. control 150 ± 9.55s, $P = 0.0326$). Pre-treatment with B6 significantly reduced the immobility time during FST (day 7, 109 ± 16.4s, $P < 0.001$; day 15, 124 ± 12s, $P < 0.001$ vs. levetiracetam alone), these changes were similar to imipramine, treatments did not change the locomotor activity. However, following ALA pre-treatment, the locomotor activity declined and neither of ALA doses reduced immobility time during FST. During NSFT, pre-treatment with B6, and ALA similar to imipramine decreased latency; B6 and ALA 20 mg/kg increased food intake compared to levetiracetam alone. **Conclusion**: While B6 pretreatment clearly prevented depressive-like behavior induced by levetiracetam, ALA 20 mg/kg showed antidepressant-like effect only in NSFT. Supplements are recommended for further evaluation to prevent depression comorbidity of antiepileptic drugs.

Keywords: Antiepileptic, depression, levetiracetam, Vitamin B6, α-lipoic acid

INTRODUCTION

About 50 million individuals globally suffer from epilepsy that is a chronic neurological disorder. Commonly, seizures can be successfully managed by anticonvulsant drugs in patients, whoever at least in 25% of patients seizures are resistant to therapy.[1] Depression is a serious problem which is generally undiagnosed or sometime left untreated among the patients with epilepsy.[2] Some patients may develop symptoms of depressive because of the adverse effects of epilepsy treatments (i.e., antiepileptic drugs or surgery).[3] Depression as an adverse drug reaction (i.e., iatrogenic depression) has been reported regularly for some antiepileptic drugs.[3,4] For instance, topiramat especially in rapid titration has been associated with depression, and levetiracetam (Lev) with emotion liability.[4] Lev or alpha-ethyl-2-oxo-1-pyrrolidine acetamide is an antiepileptic agent first approved by the FDA in 1999 as an adjunctive drug for the treatment of refractory partial epilepsy in adults. It is the most frequently used drug not as adjuvant in partial seizer, it has been also approved for monotherapy of partial seizure.[5] Lev is different from common antiepileptic drugs through its mechanisms of action and pharmacologic properties.[6] This drug binds to synaptic vesicle protein 2A and modulates the synaptic vesicle exocytosis and inhibits the pre-synaptic neurotransmitter release.[6] Lev has also been related with the highest prevalence of psychiatric

events (16%), especially depression, compared to other second-generation antiepileptic drugs.[7]

However, adding the common antidepressant drugs to the treatment regime in patients with epilepsy decreases the seizure threshold. Clinical data regarding safety and efficacy of antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors in patients with seizure are still poor.[8] In addition, two preclinical studies even concluded that SSRI class of antidepressant drug is ineffective in alleviating the depression related with chronic epilepsy.[9,10] Suggesting that depression in epilepsy might have different mechanisms beyond changes in the serotonergic pathways.[10] The disparity of neurotransmitters gamma-aminobutyric acid (GABA), glutamate, serotonin, and norepinephrine that are usually seen in epileptic patients might be related to depression initiation.[2]

A meta-analysis has recently shown that Vitamin B supplements might be related with the reduced risk of depression; specially in female individuals.[11] There are also animal evidence that emphasis the beneficial effects of Vitamins B6 in depression induced by dexamethasone, also as an adjuvant to antidepressant drugs such as clomipramine and venlafaxine.[12,13] Vitamin B6 is a water-soluble vitamin, with low toxicity as it is metabolized and excreted rapidly from the body. Vitamin B6 includes three pyridine derivatives, pyridoxine, pyridoxal, and pyridoxamine. While pyridoxal 5-phosphat (PLP) is the most active form and an essential cofactor for amino acid decarboxylase enzyme that synthesis the neurotransmitters involved in depression, such as dopamine, norepinephrine, and serotonin.[14] PLP is also an essential for decarboxylation of glutamine to GABA that is a main inhibitory neurotransmitter. Therefore, Vitamin B6 deficiency by decreasing GABA concentration in the central nervous system (CNS) could increase the risk for seizure.[15]

In addition, neuro-oxidative changes and mitochondrial dysfunctions have been reported as important factors related to the development of depression and with the neurobiology of this mental disorder.[16] Animal studies have previously proved the beneficial effects of creatine and α-Lipoic acid (ALA) in depression initiated by dexamethasone;[17] therefore, ALA is suggested as a new treatment for depression.[18] ALA, also known as thioic acid, is a naturally occurring antioxidant in the body that acts as an essential cofactor of mitochondrial pyruvate dehydrogenase. The effects of this antioxidant in human body contribute to oxidative homeostatic effects including free radical scavenger, reduction of lipoid peroxidation, as a cofactor, and chelation of metals.[19,20] In the CNS, pre-clinical studies have defined an anti-inflammatory effect of ALA also the inhibition of neuronal damage that is produced by reactive oxygen species imbalance.[19,21]

Following depression disorders initiated by seizure or the antiepileptic drugs, adding a common antidepressant drug should be with caution. In order to prevent the various complications like polypharmacy, or the risk of deteriorating the seizure disorder. Vitamin B6 as a cofactor for decarboxylase is important in the synthesis of neurotransmitters,[14,22] and ALA as a mitochondrial cofactor that prevents neuronal damage.[20] The possible antidepressant effects of these two supplements have been proven earlier.[12,13,19,23] Since Lev is one of antiepileptic drugs that may increase the risk of depression in the patient, introducing a complementary medicine to prevent depression would be valuable. The preventive effects of ALA and Vitamin B6 on Lev-induced depression have not been studied before. Therefore, in this study, the aim was evaluating the preventing effect of ALA and vitamin B6 from depressive–like behavior induced by Lev in mice.

MATERIALS AND METHODS

Animals

Male NMRI mice (weighing 25 ± 3 g, 6–8 weeks old) were used and housed at room temperature 21 ± 2°C, on a 12–12 h light-dark cycle (lights on at 6 AM), with free access to standard mice chow and water (supplied from filtered and disinfected drinking water). Animals were placed in the experimental room 24 h before the test for acclimatization. All the experiments were accomplished between 8 AM and 1 PM in the pharmacology laboratory. All animal procedures were performed in accordance with guidelines for the Care and Use of Laboratory Animals issued by The National Ethical Committee of Iran (Ethical No: IR.MUI.REC.1399.238). Mice weight changes were evaluated during the study (the % weight change was evaluated after 7 and 14 days), all the efforts in the experiments were made to minimize animal suffering and to reduce the number of animals used in the experiments.

Chemicals

Chemicals included Lev that was purchased from Amin Chemical & Pharmaceutical Company, Iran, ALA (Sigma-aldrich, Germany), Vitamin B6 (pyridoxine HCl, 200 mg/mL, Caspian Tamin Industry, Iran) and the reference antidepressant drug imipramine hydrochloride (Sigma-aldrich, Germany).

Study Design

The study comprised of six animal groups with seven animals in each group: Lev (20 mg/kg) alone group, the dose was based on our pilot studies and previous studies;[24] three groups that were pretreated with ALA 20, or 40 mg/kg,[17] or Vitamin B6 100 mg/kg,[12] the control positive group was pretreated with imipramine (10 mg/kg).[25] All the drugs were diluted in (0.9% saline) and were administered intraperitonealy, the control group received 0.9% saline. The volume of drug administration was 10 ml/kg.

Animals were injected daily for 14 consecutive days' pre-treatments were performed 30 min before Lev administration [Table 1]. The locomotor test and the forced swimming test (FST) were performed on days 7 (before the daily injections) and 15 (24 h after the last injection) in the same group of animals, the novelty suppressed feeding test (NSFT) was performed on day 16.

Locomotor Test

Mice locomotor activity was measured at the beginning of the behavioral experiments by an open field (40 × 40 × 40 cm) (Borj Sanat, Iran) that was divided into 15 zones by red beams crossing over the arena floor. Mice were gently put at one corner and allowed to explore the arena for 3 min,[26-28] by passing through

Table 1: Research protocol timeline

Days	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Treatments	-	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	-	-
Locomotor test	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	✓	-
FST	-	-	-	-	-	-	-	✓	-	-	-	-	-	-	-	✓	-
NSFT	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	F	✓

✓: treatment or experiment performed, -: no treatment or experiment, F: fasting at the end of behavior tests, FST: Forced swimming test, NSFT: Novelty suppressed feeding test

the beams the number of zone entries (crossing) were counted automatically and hind-leg rears were recorded manually. Total activity, that is the sum of number of horizontal (crossing) and number of vertical movements, was calculated for each mouse.[26]

FST

Mice were forced to swim in a 2-liter glass beaker (14 × 18 cm) filled with 25°C water (12.5 cm depth) for 6 min. The first 2 min after putting the mouse in water was considered for the habituation period and the immobility time was measured during the last 4 min of the test. The immobility time that indicates animal despair behavior was considered when no additional activity was observed in animals except those required to keep their head above the water.[26,29] The whole experiment was recorded by a camera and analyzed later. After the experiment, animals were dried carefully to avoid hypothermia and returned to their home cage.

NSFT

The test was performed in a plexiglas box (45 × 45 × 20 cm) that was covered with 0.5 cm of wooden bedding.[30] Three pieces of mouse chow were weighed and placed in the center of the apparatus on a Petri dish. Mice were deprived from food on day 14 with no change in water supply after FST and after 17 h the test started (day 15). Each mouse was located in the corner of the box, the latency to feed the pallet was recorded, and finally after 20 min, the total amount of food consumed was measured by weighing the remaining chow. At the end, the mice were returned to their previous cage with free access to food and water.

Data Processing and Statistical Analysis

All statistical evaluation and data processing were carried out using Excel 2010 and the GraphPad Prism 8 software (La Jolla, CA, USA). Results are expressed as group mean ± SEM to evaluate the effect of treatments regardless of time on the behavioral tests one-way analysis of variance (ANOVA) was performed, followed by Tukey's multiple comparison tests. The two-way ANOVA was performed considering the two factors of treatment and week of therapy on the subjects during the locomotor activity test and FST. Values of $P < 0.05$ were defined as statistically significant.

RESULTS

Weight Change during 14 Days' Protocol

As shown in Figure 1, Lev treated animals did not gain weight after 14 days of therapy, and the weight change was significantly lower than the control group (5.9 ± 2.3%, vs. 14 ± 1.6%, F(6,51)=4, $P = 0.0358$). Only the weight changes following imipramine pre-treatment were insignificant compared with the control group.

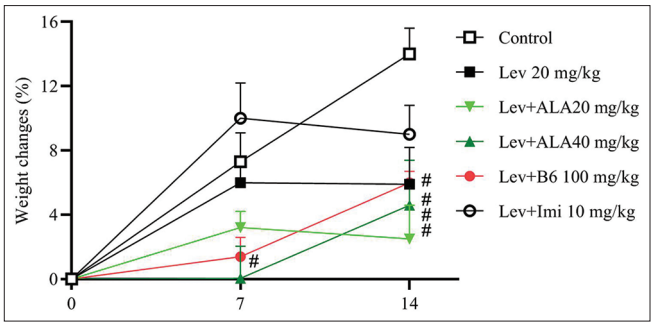

Figure 1: The percentage of body weight change after 7 and 14 days. Control animals; normal saline. The results present mean ± SEM, and analyzed by ANOVA, followed by Tukey's multiple comparison tests. #$P < 0.05$ compared with the control group. Lev: levetiracetam, ALA: α-lipoic acid, Imi: imipramine

The Effect of B6, or ALA Pretreatments on the Locomotor Activity

Locomotor activity results are presented in Table 1, the two-way ANOVA analysis showed that treatments affected the results (F(5,85)=10.69, $P < 0.0001$), but day of treatment has no effect on the results (F(1,85)=1.97, $P = 0.1641$). The effects of treatment differences regardless of week, after the 1st week, there was no difference in the locomotor activity following Lev alone administration, but after ALA pretreatment, there was a significant decrease in locomotor activity compared to the control group and compared to Lev alone, while no locomotor activity change was observed during pretreatment with B6, or imipramine compared with the control group [Table 2].

Table 2 shows following the 2nd week that locomotor activity of Lev alone was not significantly different from control, ALA 20 mg/kg pre-treatment did not significantly reduce locomotor activity, but ALA 40 mg/kg pre-treatment significantly reduced it compared to control and Lev alone. There was no significant change in locomotor activity following B6 or imipramine pre-treatment.

The Effect of B6, or ALA Pretreatments on FST

Figure 2 presents the result of FST, the two-way ANOVA analysis showed that treatments affected the results (F(5,85)=32, $P < 0.0001$), but day of treatment has no effect on the results (F(1,85)=2.47, $P = 0.1194$). The effects of treatment differences regardless of week, as shown in Figure 2,

Table 2: Effect of Vitamin B6 and ALA pre-treatment on locomotor activity following Lev administration

Groups (n=7)	Locomotor activity (units)	
	7 days	14 days
Control	175±16.6	152±11.4
Lev 20 mg/kg	189±16.0	175±15.5
Lev 20+ALA 20 mg/kg	88.7±16.2$^{\#\#,**}$	127±20.7
Lev 20+ALA 40 mg/kg	82.0±11.0$^{\#\#,**}$	72.0±19.1$^{\#,**}$
Lev 20+B6 100 mg/kg	172±14.9	111±21.6
Lev 20+Imi 10 mg/kg	156±19.0	144±19.3

Total activity = (horizontal+vertical) movements. Control animals; normal saline. Results are expressed as group mean±SEM and analyzed by ANOVA followed by Tukey's comparison test. $^{\#}P<0.05$, $^{\#\#}P<0.01$ compared with control group, $^{**}P<0.01$ compared with Lev alone group. Lev: levetiracetam, ALA: α-lipoic acid, Imp: imipramine

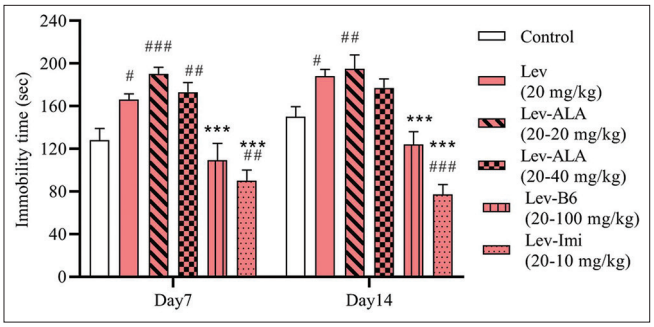

Figure 2: Effect of Vitamin B6 or ALA pre-treatment on Lev immobility time during the forced swimming test performed on days 7 and 15. Control animals; normal saline. The results present mean ± SEM, and analyzed by ANOVA followed by Tukey's multiple comparison tests. $\#P < 0.05$, $\#\#P < 0.01$, $\#\#\#P < 0.001$ compared with the control group, $***P < 0.001$ compared with Lev alone group. Lev: levetiracetam, ALA: α-lipoic acid, Imi: imipramine

the immobility time during FST increased after the 1st week of lev administration (166 ± 5.63s vs. control 128 ± 10.5s, F(5,44)=17, P = 0.020), which indicated depressive-like behavior. Following pretreatment with ALA 20 or 40 mg/kg, immobility time increased even more (190 ± 6.57s, $P < 0.001$ and 173 ± 9.19s, P = 0.0083; F(5,44)=17 respectively) compared to the control group. After pre-treatment with B6 immobility time during FST reduced significantly [Figure 2; 108.6 ± 16.4s, F(5,44)=17, $P < 0.001$ vs. Lev alone]. The decrease in immobility time during FST was similar to the pretreatment with imipramine results.

The immobility time in the FST on day14 is depicted in Figure 2. Administrating Lev increased the immobility time (187.8 ± 6.45s vs. control 150 ± 9.55s, F(5,41)=18, P = 0.0326). Following ALA 20 or 40 mg/kg pre-treatment, there was no change in the immobility time compared to Lev alone group. On the other hand, B6 pre-treatment alike imipramine significantly reduced immobility time in FST [Figure 2, 124 ± 12s, F(5,41)=18, $P < 0.001$ vs. Lev alone].

The Effect of B6, or ALA Pretreatments on NSFT

Latency to food consumption in NSFT is presented in Figure 3a, Lev significantly increased the latency (181 ± 31.9s vs. control 65.6 ± 8.77s, F (5,37) = 6.422, $P < 0.001$). Pre-treatment with ALA or B6 significantly reduced latency compared to Lev alone that were similar to pre-treatment with imipramine (85 ± 10.1s, F (5,37) = 6.422, P = 0.0023, vs. Lev alone group). Figure 3b shows total food intake after 20 min in NSFT, Lev treatment significantly reduced the food intake (5.58 ± 1.22 mg/g body weight, vs. control 13.3 ± 1.17 mg/g body weight, F (5,38) = 6.336, P = 0.002). While pre-treatment with ALA 20 mg/kg increased food consumption (14.5 ± 2.54 mg/g body weight, F (5,38) = 6.336, P = 0.0015 vs. Lev alone group) ALA 40 mg/kg pre-treatment was not effective. Administrating B6 also increased food consumption (12.6 ± 1.18 mg/g body weight, F (5,38) = 6.336, P = 0.0106 vs. Lev alone group) that was similar to the increase in food intake following imipramine pre-treatment.

DISCUSSION

Our results proved that administrating lev 20 mg/kg induced depressive-like behavior in mice and pre-treatment with B6 and to some extent ALA prevented Lev from initiating depressive-like effects. In this experiment, FST was chosen as an acute model of depression and NSFT was chosen to evaluate the chronic effect of the treatments on depression in mice.[31,32] The FST has been used for antidepressant screening of drugs for decades. In the FST, the drugs with antidepressants effect can efficiently reverse the immobility behavior. On the other hand, repeated FST could be considered to evaluate antidepressant effects, with the advantage of reducing the number of animals used for drug screenings.[33] The NSFT involves measuring the eating latency in a new environment that imitates the level of anxiety. While measuring the change in food intake translates the change in appetite as another endophenotypes of depression.[32]

During the 1st week of treatment with Lev alone or pre-treatment with ALA 20 mg/kg or B6, the animals gained weight although it was absent during ALA 40 mg/kg pretreatment. However, animals failed to gain weight at the 2nd week of therapy. Since many factors can influence rodents weight changes, the underling mechanism needs to be carefully addressed.[34] However, it has been shown previously that Lev can induce weight loss in patients.[35]

Lev clearly caused depressive-like effect in mice as it was depicted from the increased in the immobility time in the FST after 1 week and 2 weeks of administrations, and the increased latency and decreased food consumption in NSFT.

Previously, it was proven that patients taking Lev have experienced considerably more psychiatric side effects than patients treated with other antiepileptic drugs.[7] In addition, Kaufman and colleagues (2013) have report in a case without prior history of affective disorder an obvious dose-dependent LEV-induced major depression with the risk for suicide attempt.[36] In mice, it was shown that treatment with Lev 40 mg/kg for 15 days in kindled mice significantly increased immobility time in the tail suspension test compared with naïve animals, and significantly reduced the sucrose preference that also indicates anhedonia.[37] Administrating Lev alone in mice or in combination with pentylenetetrazole-induced kindling has significantly increased the immobility time during FST.[38]

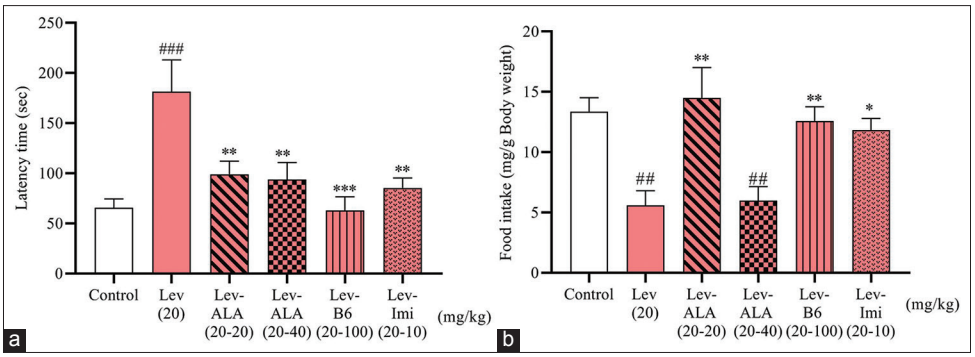

Figure 3: Effect of Vitamin B6 or ALA pre-treatment on Lev latency (a) and food intake (b) during novel feeding test after 14 days. Control animals; normal saline. The results present mean ± SEM, and analyzed by ANOVA followed by Tukey's multiple comparison tests. $\#\#P < 0.01$, $\#\#\#P < 0.001$ compared with the control group, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ compared with Lev alone group. Lev: levetiracetam, ALA: α-lipoic acid, Imi: imipramine

Depressive-like behavior was not initiated in mice following pretreatment with B6. During the FST immobility time measured after 1 and 2 weeks reduced, latency during the NSFT reduced and animals' appetite increased. The antidepressant-like effect of B6 is supported by ample animal studies.[12-14] Studies have previously shown that among the supplement's Vitamin B6 is highly implicated with the cause and cure of depression and is involved in the control of mood. Actually, pyridoxine regulates neurotransmitters that control depression and anxiety.[14,39] Deficiency in pyridoxine increases the homocysteine levels that is linked to seizures, and depression.[39] Vitamin B_6 changes homocysteine metabolism by decreasing the activity of serine hydroxymethyltransferase and by inhibiting homocysteine catabolism.[40]

On the other hand, ALA 20 mg/kg reversed latency and increased food consumption during NSFT, following Lev administration, that shows its efficacy in preventing depressive-like effect. However, this preventive effect was not observed during FST following ALA pre-treatment. This could be a direct result of a noticeable reduction in the locomotor activity that persisted for 14 days after ALA pre-treatment. According to the previous studies, ALA alone does not cause important changes in the locomotor activity.[17] Furthermore, locomotor activity changes following Lev administration alone was absent [Table 2]. This change would not be considered toxic but may be a result of sedating effect, or another pharmacological interaction that needs more evaluations. Therefore, according to the present experiments, FST was not a reliable method for evaluating anti-depressant effects of ALA and Lev coadministration. On the other hand, the NSFT chronic model was more appropriate but the less food consumption following the pre-treatment with ALA 40 mg/kg might also be related to less locomotor activity. Virtually all antioxidants, including endogenously present ALA and melatonin,[41] exogenous anticonvulsive and neuroprotective ingredients, such as ascorbic acid,[42] curcumin,[43] and synthetic radical scavengers, like aspalatone,[44] have shown neuroprotective effects against oxidative stress initiated by proconvulsive substances that are used in animal models of epilepsy.[45] The previous studies have proved the beneficial anti-seizer activity of ALA in *in vivo* and *in vitro* models, due to its antioxidant capacity.[45] In addition, pre-treatment with ALA might also prevent comorbidity mood disorders that warrants more evaluations.

Our study limitation was that the molecular mechanism involved in B6 or ALA inhibiting depression initiation by Lev was not evaluated.

CONCLUSION

This animal study proved that Vitamin B6 prevented depressive-like behavior induced by Lev. ALA interaction with Lev decreased locomotor activity and depressive like behavior was only relevant by NSFT. Since depression is a comorbidity of seizure and antiepileptic drugs such as Lev, pre-treatment with safe supplement drugs like Vitamin B6 is suggested for further evaluations.

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The authors certify that no conflicts of interest in relation to this article exists.

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