Title: Effects of Pyridoxine on Preventing Behavioral Disturbances Induced by Levetiracetam in Adult Patients with Seizure Disorders

Authors: Fatemeh Zarei Hajiabadi[1], Vajiheh Aghamollaii[2,*], Padideh Ghaeli[3,*], Abolfazl Mohammadi[4], Samira Chaybakhsh[5], Sana Khajehpour[6]

1. *Clinical Pharmacist, School of Pharmacy, Tehran University of Medical Sciences (TUMS), Tehran, Iran.*
2. *Neuropsychiatry Department, Roozbeh Hospital, Tehran University of Medical sSciences (TUMS), Tehran, Iran.*
3. *Clinical Pharmacy, Roozbeh Hospital and School of Pharmacy, Tehran University of Medical Sciences (TUMS), Tehran, Iran.*
4. *Clinical Psychology, Department of Psychiatry, Tehran University of Medical Sciences (TUMS), Tehran, Iran.*
5. *Research Center for Rational Use of Drugs, Tehran University of Medical Sciences (TUMS), Tehran, Iran.*
6. *Faculty of Pharmacy, Department of Biomedical and Pharmaceutical Sciences, Idaho State University, Idaho, USA.*

***Corresponding Author**: Vajiheh Aghamollaii, Neuropsychiatry Department, Roozbeh Hospital, Tehran University of Medical sSciences (TUMS), Tehran, Iran. ; Padideh Ghaeli, Clinical Pharmacy, Roozbeh Hospital and School of Pharmacy, Tehran University of Medical Sciences (TUMS), Tehran, Iran. Email: vajiheh102@gmail.com, mmppg@yahoo.com.

To appear in: **Basic and Clinical Neuroscience**

Received date: 2020/06/04

Revised date: 2021/04/17

Accepted date: 2023/09/27

Please cite this article as:
Zarei Hajiabadi, F., Aghamollaii, V., Ghaeli, P., Mohammadi, A., Chaybakhsh, S., Khajehpour, S. (In Press). Effects of Pyridoxine on Preventing Behavioral Disturbances Induced by Levetiracetam in Adult Patients with Seizure Disorders. Basic and Clinical Neuroscience. Just Accepted publication Jul. 10, 2023. Doi: http://dx.doi.org/10.32598/bcn.2023.2503.1

DOI: http://dx.doi.org/10.32598/bcn.2023.2503.1

Abstract

Objective: Behavioral disorder is known as one of the most common side effects of levetiracetam (LEV). Previous studies in children and adolescents have noted the potential positive effects of pyridoxine in preventing these disorders. Pyridoxine (Vitamin B_6) is a water-soluble vitamin playing a pivotal role as a co-factor in regulating more than 100 enzymatic reactions such as GABA and serotonin synthesis and catabolism. This study aims at investigating the effects of pyridoxine on behavioral disorders, including depression, anxiety, and stress caused by levetiracetam.

Method: A total of 38 patients who were prescribed levetiracetam by a neurologist were enrolled in the study following taking informed consent. They were randomly divided into two groups. A group of 19 people received pyridoxine 40 mg twice daily in the first two weeks and 40 mg 3 times per day for the next two weeks known as the intervention group. The remaining patients were taking only levetiracetam known as the control group. DASS 21 questionnaire was used to measure levetiracetam induced depression, anxiety, and stress at weeks 0 and 4.

Results: In this study, 19 patients received LEV in different doses, and 19 received LEV plus pyridoxine 40 mg twice daily for 2 weeks following a 40 mg three times daily for two more weeks. After 4 weeks of treatment with both LEV and LEV plus pyridoxine, the results revealed that two treatments equally induced the LEV induced symptoms. After 4 weeks of treatment, the results of this study did not show any significant differences between the intervention and control group.

Conclusion: This study suggests that pyridoxine may not be effective in preventing depression, anxiety, and stress-induced by levetiracetam in adult patients who are suffering from seizure disorders and are on levetiracetam.

Keywords: Pyridoxine, Vitamin B6, Levetiracetam, Depression, Anxiety, Stress.

1. Introduction

Levetiracetam (LEV) is a second-generation antiepileptic drug that has been approved for the treatment of partial seizures, myoclonic seizures, and tonic-clonic seizures. In 2000, the FDA approved the use of the oral formulation of levetiracetam as adjunctive therapy for the treatment of focal seizures, myoclonic seizures, and primary generalized seizures. The FDA approved intravenous Levetiracetam (LEV) in 2006 for use in patients older than 15 years of age, as adjunctive anticonvulsant therapy when the oral formulation is not tolerated. In Europe, it is approved either as a single agent or as an add-on treatment for partial seizures, tonic-clonic seizures, and myoclonic seizures (Kumar et al., 2020).

Neuro-behavioral changes are among the most common side effects of LEV and include somnolence, fatigue, mood swings, depression, headache, irritability, agitation, memory loss, aggression, cognition disorders, and suicidal thoughts. It has been reported that patients who are on LEV experience psychiatric/behavioral side effects more than those taking other antiepileptic medications (Weintraub et al., 2007). Behavioral side effects are increasingly being recognized and can affect around 13% of patients (Harden,2001), particularly patients with preexisting behavioral issues, and this can lead to LEV discontinuation (White et al., 2003). Adverse events were usually mild to moderate, and most frequently occurred during the first four weeks of treatment based on reports (Harden,2001).

Levetiracetam is a well-tolerated and effective anti-epileptic medicine. Although it generally has a good side-effect profile, psychiatric side effects seen in up to 13.3 percent of adults and 37.6 percent of pediatric patients can be significant. Of these, severe symptoms such as depression, agitation, or hostility, and psychotic behavior are observed in 0.7 percent of patients (Delanty et al., 2012).

Pyridoxine (vitamin B_6), a water-soluble vitamin, exerts its cofactor action through catalyzing enzymatic reactions, mainly in the synthesis of neurotransmitters. Previous reports have indicated that pyridoxine (vitamin B_6) can ameliorate behavioral side effects related to LEV therapy in children and adolescents (Major et al., 2008). A retrospective study in UAE has suggested that this medication may be useful in adults as well (Alsaadi et al., 2015).

A retrospective review of electronic medical records were conducted, identifying all the patients from the Creighton University Epilepsy Center Clinic from 2011 to 2015. It aimed to identify those who were on Levetiracetam and were then started on pyridoxine by Epileptologists. It was identified that 45 such patients out of 380 patients on Levetiracetam. These 45 patients had significant behavioral side effects and were started on Pyridoxine 100mg per day for control of these symptoms. Behavioral side effects were seen in 11.8% of patients treated with Levetiracetam, and these effects were usually seen within the first 4 weeks of initiation of

Levetiracetam therapy. Of those 45 who received Pyridoxine, 42 (93.3%) patients continued to be on Levetiracetam as they had significant improvement in their behavioral symptoms. (Sajja et al., 2017)

A recent randomized, case-control trial included patients receiving LEV as a monotherapy treatment. Patients were divided into 2 groups, according to whether they were treated with LEV only (group 1) or LEV with supplemental pyridoxine (group 2). Changing the dose or suspending LEV were not needed in those patients (92%) who initiated pyridoxine after one month of LEV treatment ($P < 0.001$), and behavioral adverse effects improved after 9.06 ± 3.05 days of pyridoxine add-on regimen. There were no complaints about pyridoxine toxicity among patients (Marino et al., 2018). However, it has been noted that peripheral neuropathy may be associated with a high intake of pyridoxine (Calyton, 2006).

Our goal was to assess the potential benefits of the use of pyridoxine as as adjuvant treatment for the prevention of behavioral side effects induced by LEV in adults.

2. Methods and Materials

Based on previous studies and a pilot study that we conducted in Roozbeh Neurology Clinic, a total of 38 patients who were referred to Roozbeh Hospital outpatient Neurology clinic from May 2017 to July 2018 were studied. Sample size is calculated with the formula provided below.

$$n = \frac{[Z(1-\frac{\alpha}{2} + Z(1-\beta)]^2(s_1{}^2 + s_2{}^2)}{d^2} = \frac{[1.96 + 0.84]^2 * (9 + 49)}{25} \cong 19$$

α=0.05
β= 0.2
S_1= 3
S_2= 7

All subjects were about to start Levetiracetam for a seizure disorder, prescribed by Dr.Vajiheh Aghamolaei.MD (Neurologist) . They were randomly allocated into two groups receiving either LEV or LEV+pyridoxine.using blocked randomization table. Inclusion criteria for this study included patients between 18 to 65 years of age prescribed with LEV by a psychiatric specialist for their current implications.

Patients with either of these implications were excluded from this study: sensitivity to LEV or pyridoxine, neurological illnesses including Multiple Sclerosis and Parkinsonism, diagnosed psychiatric disorders and history of behavioral disturbances,

renal and hepatic insufficiency, having received LEV before the initiation of the study, failure to cooperating with researchers in the study for filling the questionnaire (Jafari et al., 2017).

Patients were allocated into two subgroups using a blocked randomization method. Patients in the first group received Levetiracetam and pyridoxine. The dose of Pyridoxine was 40 mg twice daily for two weeks, which increased to 40 mg three times per day after 2 weeks. Patients in the second group only received levetiracetam.

Researchers provided a full explanation of the protocol design following providing written informed consent. This trial was approved by the Ethics Committee of the Faculty of Pharmacy at Tehran University of Medical Sciences. All phases of this study were performed according to the declaration of Helsinki on ethical principles for medical research involving human subjects.

The DASS 21 (depression, stress, and anxiety scale) questionnaire is a self-report questionnaire, which was used to assess depression, anxiety, and stress level at baseline and after 4 weeks of treatment with either LEV or LEV plus pyridoxine. This questionnaire contains 21 questions with seven questions assessing depression (questions 3,5,10,13, 16,17, and 21), seven questions evaluating anxiety (questions 2,4,7,9,15, 19, and 20) and seven questions asking about the stress level (questions 1,6,8,11,12,14,18). Participants answered the questions on a four-step Likert-scale answer sheet based on what they felt or thought at the moment. The items were rated as follow: (0) Did not apply to me at all; (1) Applied to me to some degree, or some of the time; (2) Applied to me to a considerable degree or a good part of time, and (3) Applied to me very much or most of the time. Originally, the scale was in English; however, an approved standard Persian translation was used in this study (Asghari et al., 2008). Patients were followed up at the clinic after 4 weeks and filled DASS21 questionnaire again to assess the effects of Pyridoxine supplementation on preventing depression, anxiety, and stress.

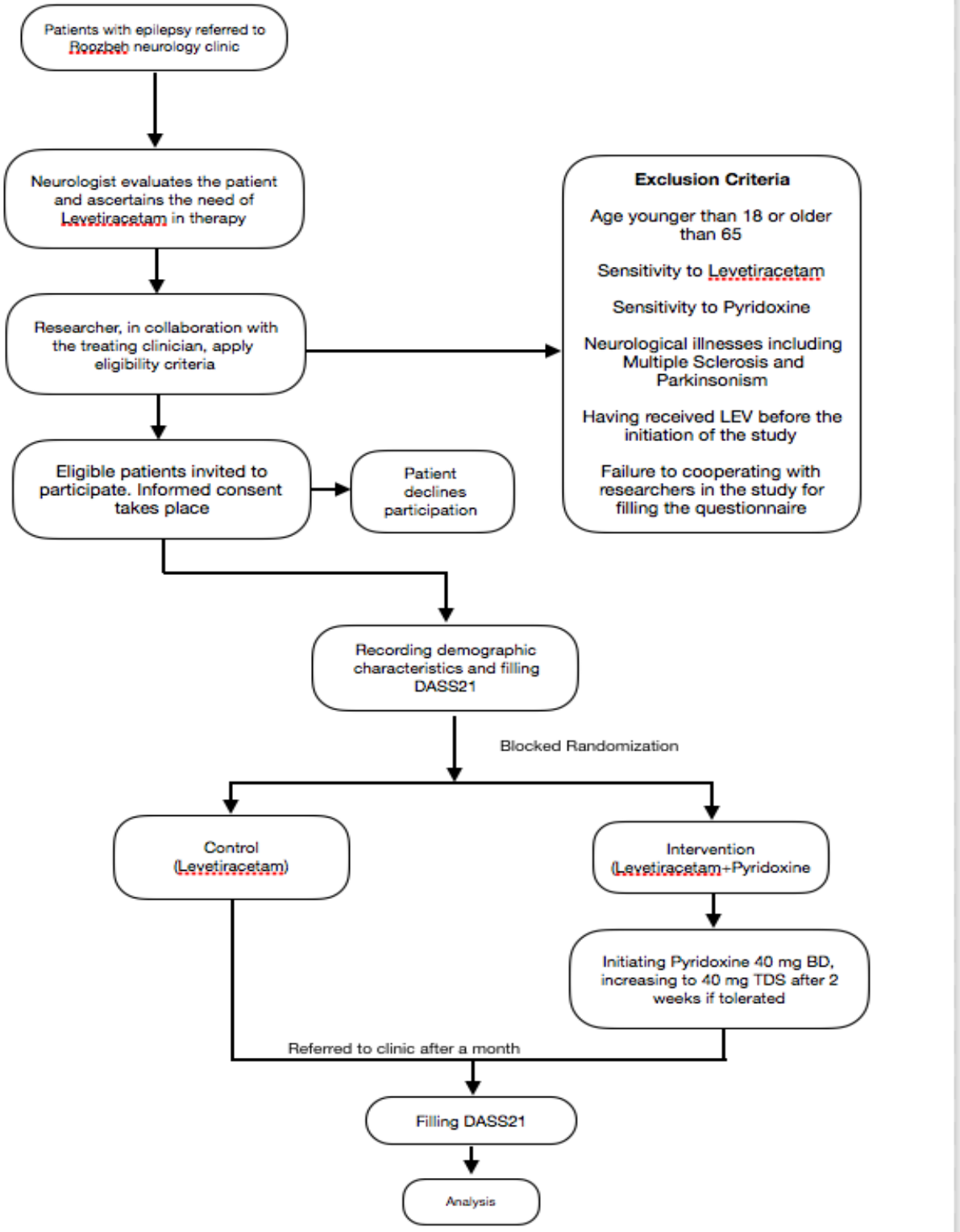
Data analysis was done by SPSS-21 statistical software. The changes in DASS 21 measurements were detected at weeks 0 and 4 between the 2 groups. $p < 0.05$ deemed as statistical significance.

3. Results

The demographic characteristics of participants are as shown in table 1. In this study, 48 patients were screened for the study, of whom 10 were excluded. In total, 38 patients completed the trial; LEV monotherapy was used for 19 patients (mean age in years ± standard deviation was 36.21 ± 9.5) and 19 were received LEV with add-on pyridoxine (mean age in years ± standard deviation was 31.9 ± 8.34). There were no

statistically significant differences between the two groups in terms of demographics at baseline.

Patient Flow Diagram



Variable	LEV + Pyridoxine Group	LEV Only Group	P (2-tailed)
Age (Range) Mean (SD)	19 – 45 34.84 (9.31)	21 – 55 49.95 (21.36)	0.144
Gender (Male) No (%)	13 (68.42)	12 (63.15)	0.723
The disease that LEV prescribed for (%) TLE (Temporal Lobe Epilepsy) GTC (Generalized tonic-clonic seizure) FLE (Frontal Lobe Epilepsy) Myoclonic Seizure Others	 52.63 15.7 0 21.05 10.52	 52.63 10.52 26.31 5.26 5.26	
LEV daily dose (%) 250 mg daily 500 mg daily 750 mg daily 1000 mg daily	 21.05 57.9 5.26 15.78	 26.31 52.63 0 21.05	1.000
DASS 21 Total Score Mean (SD)	18.58 (9.61)	19.32 (14.53)	
DASS 21 Total Score for Depression Mean (SD)	5.84 (4.35)	5.16 (5.37)	
DASS 21 Total Score for Anxiety Mean (SD)	6.37 (3.67)	5.9 (4.68)	
DASS 21 Total Score for Stress Mean (SD)	8.79 (4.43)	8.26 (5.48)	

Table 1, Demographic characteristics of participants

Table 2 shows the total scores of DASS 21 questionnaire between two groups at baseline and after 4 weeks.

Table 2. Mean (SD) total scores of patients in each group at baseline and after 4 weeks

Groups Week	LEV + Pyridoxine Mean (SD)	LEV Only Mean (SD)
0	18.59 (9.16)	19.31 (14.52)
4	20.00 (10.11)	20.94 (12.07)

The calculated p-value (p=0.588) between the patients receiving only LEV and patients receiving LEV + pyridoxine showed no significant difference between the two groups of treatment. In summary, there were no significant differences between the control and intervention group in depression, anxiety, and stress, and the total score of DASS21 changes after 4 weeks of Levetiracetam use and pyridoxine did not improve the LEV adverse effects in terms of depression, anxiety, and stress (Fig. 1). No clear adverse effects were reported during the study.

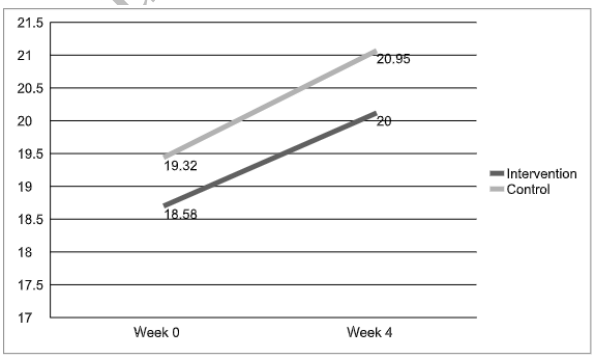


Figure 1. DASS21 measurements at week 0 and 4 between two groups

4. Discussion

Anti-epileptic drugs that are known as enzyme-inducers (phenytoin or carbamazepine) can potentially alter the metabolism pathways, including vitamin levels. Mintzer et al. showed that anti-epileptic drugs (AEDs) induce B vitamins

deficiency regardless of being enzyme-inducer or non-inducer. However, treatment with inducing AEDs causes severe pyridoxine deficiency commonly, which is the main contributing factor of polyneuropathy, as well as other chronic health difficulties (Mintzer et al., 2012). In critically ill adults with pyridoxine deficiency, vitamin B6 supplementation has a very little associated risk and should be considered in those patients with refractory seizures. However, these results represent a case series and not a controlled trial. In children with seizures being refractory to conventional antiepileptic drugs, vitamin B6 insufficiency has been shown as a potential cause of seizures. In three cases of adults suffering from refractory seizures, vitamin B6 therapy could resolve the persisted seizures in 2 days (Gerlach et al., 2011).

To our knowledge, this is the first clinical trial that studied the potential benefits of pyridoxine supplementation in the treatment of LEV- induced behavioral side effects in the adult population.

Previous reports in the pediatric population have demonstrated the potential beneficial effect of pyridoxine in controlling LEV-induced behavioral symptoms. Miller et al. (Miller et al., 2002) were able to control the behavioral disturbances caused by LEV entirely, in 5 of 6 children aged between 2 to 10 years old, by supplementing pyridoxine at an average dose of 7 mg/kg/day. In another study to examine the use of pyridoxine, Major et al. found that among twenty-two pediatric patients treated with pyridoxine after being on LEV due to behavioral side effects, a significant behavioral improvement was observed in nine (41%), no effect in eight (36%), deterioration in four (18%), and an uncertain effect in one. (Major et al., 2008). There is no known pharmacokinetic or pharmacodynamic interaction between LEV and vitamin B6. Pyridoxine has been used to treat other medical conditions, such as premenstrual depression (Wyatt et al., 1999). On the other hand, pyridoxine has been prescribed-based on our current understanding- for the treatment of other underlying metabolic disorders. For example, pyridoxine-dependent epilepsy, a rare autosomal recessive error of metabolism characterized by neonatal seizures, responds to pyridoxine. Intravenous administration of 50–100 mg of pyridoxine promptly controls the seizures, but lifelong supplementation is required (5–300 mg/kg/day) (Calyton, 2006).

One of the reasons that despite the pediatric population, pyridoxine was not effective in preventing behavioral disorders in the adult population may be a higher prevalence of behavioral disorders in the pediatric population as mentioned before (Delanty et al., 2012).

Hagemann et al. in a prospective, open study showed that when LEV is added to the treatment of anxiety and depression, health-related quality of life was improved

(Hagemann et al., 2013). LEV is an add-on for children with resistant epilepsy that can control their seizures effectively with good tolerability. However, it may increase the risk of reversible neurocognitive side effects in neurologically handicapped children, so it results in a more reduced treatment response (Opp et al., 2005). In a multi-center double-blind responder-selected study it is depicted that switching from 3000 mg/day LEV add-on regimen to 1500 mg twice a day LEV monotherapy is effective and well-tolerated in patients suffering from refractory partial seizure (Ben-Menachem et al., 2000). Stephen et al. in their study found that if LEV on a median dose of 1000 mg/day was used as monotherapy for seizure, fifty percent of patients would achieve seizure freedom. Around 50% of those who discontinued LEV due to side effects developed neuropsychiatric symptoms (Stephen et al., 2011). Adjunctive LEV consumption is likely to improve psychiatric symptoms as well as life quality in patients suffering from epilepsy resistant to the drug (Lee et al., 2011). Apart from its positive pharmacological effects, LEV seems to have a negative stimulating effect mainly expressed as aggression increases, especially in patients with unsuccessful control of their seizure and patients with mental retardation. This group also observed that the behavioral side effects of LEV are not related to dose or co-medication (Helmstaedter et al., 2008). In a meta-analysis study, including all double-blind, randomized placebo control studies on 2832 patients aimed at studying the adverse reactions of LEV compared to placebo, the results show that patients receiving LEV were more prone to LEV discontinuation than placebo because of its adverse drug reactions (Verrotti et al., 2015). Despite all of the noted adverse reactions of LEV, some reports indicated that the use of LEV in the first trimester of pregnancy is safer than other epilepsy medications and the risk of major malformation in the population is between 1% to 3% with no adverse effects on child development in the long term (Chaudhry, Koren, 2014). It also did not show any interactions with other AEDs except topiramate and carbamazepine or cardiovascular drugs such as digoxin and warfarin and a low dose of contraceptive pills. All this evidence made LEV a favorable and straightforward medication in epilepsy (Patsalos, 2004)(Hovinga, 2001).

4. Conclusion

Our study demonstrated that pyridoxine did not help prevent LEV-related behavioral side effects. No harm and serious side effects were experienced by patients. This study was a short-term single center study. A further prospective, placebo-controlled, multi-center study on a more diverse population is needed to assess pyridoxine as an add-on treatment for LEV induced depression, stress, and anxiety to address unanswered questions.

Conflict of interest

None of the authors has any conflict of interest to disclose.

Acknowledgments

The authors want to thank the staff of the department of clinical pharmacy at Tehran University of Medical Sciences, Nursing staff, and department of Neurology at Roozbeh Hospital, Dr.Safoora Beik-Rasooli, Nesa Rahimi, Dr. Zahra Jahangard, and Dr. Soha Namazi for their great help and support.

5. References

Alsaadi T, El Hammasi K, Shahrour TM. (2015). Does pyridoxine control behavioral symptoms in adult patients treated with levetiracetam? Case series from UAE. Epilepsy & behavior case reports, 4,94-95.

Asghari A, Saed F, Dibajnia P. (2008). Psychometric properties of the Depression Anxiety Stress Scales-21 (DASS-21) in a non-clinical Iranian sample. Int J Psychol, 2(2),82-102.

Ben-Menachem E, Falter U. (2000). Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. Epilepsia, 41(10),1276-1283.

Chaudhry SA, Koren G. (2014). The fetal safety of Levetiracetam: a systematic review. Reproductive toxicology, 46, 40-45.

Clayton PT. (2006). B6-responsive disorders: a model of vitamin dependency. Journal of inherited metabolic disease, 29(2-3), 317-326

Delanty N, Jones J, Tonner F. (2012). Adjunctive levetiracetam in children, adolescents, and adults with primary generalized seizures: open-label, noncomparative, multicenter, long-term follow-up study. Epilepsia, 53(1), 111-119.

Gerlach AT, Thomas S, Stawicki SP, Whitmill ML, Steinberg SM, Cook CH. (2011). Vitamin B6 deficiency: a potential cause of refractory seizures in adults. Journal of Parenteral and Enteral Nutrition, 35(2), 272-275.

Hagemann A, May TW, Nieder E, Witte-Bölt K, Pohlmann-Eden B, Elger CE, et al. (2013). Quality of life, anxiety, and depression in adult patients after add-on of levetiracetam and conversion to levetiracetam monotherapy. Epilepsy research,104(1-2),140-150.

Harden C. (2001). Safety profile of levetiracetam. Epilepsia, 42, 36-39.

Helmstaedter C, Fritz N, Kockelmann E, Kosanetzky N, Elger C. (2008). Positive and negative psychotropic effects of levetiracetam. Epilepsy & Behavior, 13(3), 535-541.

Hovinga CA. (2001). Levetiracetam: a novel antiepileptic drug. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 21(11), 1375-1388.

Jafari S, Khajehpour S, Razzaghi EM, Heidari K, Soleimani M, Ghaeli P. (2017). Craving and drug reward: A comparison of celecoxib and ibuprofen in detoxifying opiate addicts. Iranian journal of psychiatry, 12(4), 229-235

Kumar A, Maini K, Kadian R. (2020). Levetiracetam. In:StatPearls [Internet]. Treasure Island (FL)

Lee J-J, Song H-S, Hwang Y-H, Lee H-W, Suh C-K, Park S-P. (2011). Psychiatric symptoms and quality of life in patients with drug-refractory epilepsy receiving adjunctive levetiracetam therapy. Journal of Clinical Neurology, 7(3), 128-36.

Major P, Greenberg E, Khan A, Thiele EA. (2008). Pyridoxine supplementation for the treatment of levetiracetam-induced behavior side effects in children: preliminary results. Epilepsy & Behavior, 13(3), 557-559

Marino S, Vitaliti G, Marino SD, Pavone P, Provvidenti S, Romano C, et al. (2018). Pyridoxine Add-On Treatment for the Control of Behavioral Adverse Effects Induced by Levetiracetam in Children: A Case-Control Prospective Study. Annals of Pharmacotherapy, 52(7), 645-649

Miller GS. (2002). Pyridoxine ameliorates adverse behavioral effects of levetiracetam in children. Epilepsia, 43, 62

Mintzer S, Skidmore CT, Sperling MR. (2007). B-vitamin deficiency in patients treated with antiepileptic drugs. Epilepsy & Behavior, 24(3), 341-4

Opp J, Tuxhorn I, May T, Kluger G, Wiemer-Kruel A, Kurlemann G, et al. (2005). Levetiracetam in children with refractory epilepsy: a multicenter open-label study in Germany. Seizure, 14(7), 476-484.

Patsalos PN. (2004) Clinical pharmacokinetics of levetiracetam. Clinical pharmacokinetics,43(11), 707-24.

Sajja K, Sankaraneni R, Galla K, Singh SP. (2017) Presented at AES annual meeting in Washington, DC. Abstract 1.308. Role of Pyridoxine (Vitamin B6) in the Treatment of Levetiracetam Induced Behavioral Effects in Epilepsy Patients.

Stephen LJ, Kelly K, Parker P, Brodie MJ. (2011). Levetiracetam monotherapy—outcomes from an epilepsy clinic. Seizure, 20(7), 554-557.

Verrotti A, Prezioso G, Di Sabatino F, Franco V, Chiarelli F, Zaccara G. (2015). The adverse event profile of levetiracetam: a meta-analysis on children and adults. Seizure, 31, 49-55.

Weintraub D, Buchsbaum R, Resor Jr S, Hirsch L. (2007). Psychiatric and behavioral side effects of the newer antiepileptic drugs in adults with epilepsy. Epilepsy & Behavior, 10(1), 105-110

White J, Walczak T, Leppik I, Rarick J, Tran T, Beniak T, et al. (2003). Discontinuation of levetiracetam because of behavioral side effects: a case-control study. Neurology, 61(9), 1218-1221.

Wyatt KM, Dimmock PW, Jones PW, O'brien PS. (1999). Efficacy of vitamin B-6 in the treatment of premenstrual syndrome: a systematic review. BMJ, 318(7195),1375-1381. 1. Demographic and clinical characteristics of patients at baseline