



## Case Report

## Does pyridoxine control behavioral symptoms in adult patients treated with levetiracetam? Case series from UAE☆

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## ABSTRACT

Behavioral symptoms are known side effects of levetiracetam. Previous case series in children and adolescents have demonstrated the potential effect of pyridoxine in ameliorating these symptoms. We retrospectively reviewed the charts of 51 patients treated with pyridoxine to control agitation and irritability following the introduction of levetiracetam. These symptoms were relieved in 34 patients (66.6%). Seventeen patients did not appear to benefit from this supplementation. This preliminary study suggests that pyridoxine might be an effective option across all ages for patients suffering from levetiracetam-induced behavioral side effects.

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## 1. Introduction

Levetiracetam (LEV) is an antiepileptic drug that is approved for use as adjunct treatment for partial epilepsy in patients aged 4 years and older, as well as for juvenile myoclonic epilepsy in patients aged 12 years and older [1,2]. Irritability and agitation are known behavioral side effects of LEV, and it is reported in almost 13% of patients across all age groups. Levetiracetam use can be associated with insomnia, agitation, anxiety, emotional lability, and hyperactivity. Some of these adverse events, however, are reported in patients with preexisting behavioral issues [3]. Furthermore, these adverse effects can lead to LEV discontinuation in a small percentage of patients [4]. Previous case series from children and adolescents have indicated that pyridoxine (vitamin B6) can alleviate behavioral side effects related to the use of LEV [5,6]. The effect seems to be modest.

In this study, we sought to explore the potential benefits of pyridoxine supplementation for the treatment of behavioral side effects induced by LEV in our patients attending the epilepsy clinic.

## 2. Methods

We retrospectively reviewed our electronic medical records to identify all patients attending our epilepsy clinic and being treated with both LEV and pyridoxine. Fifty-one adult patients were identified using pyridoxine supplementation for the management of either irritability or agitation following the introduction of LEV. Age, gender, epilepsy classification, duration of seizures, dosages of LEV and pyridoxine, and the effect of the addition of pyridoxine on behavioral symptoms were carefully analyzed. When in doubt, these patients were contacted. This study was approved by the local institutional review board.

## 3. Results

This group comprised 41 men and 47 women. Their average age was 34.2 years (SD = 11.1). The epilepsy was classified as idiopathic in 15 patients (29.5%) and as partial in 36 (70.5%). Levetiracetam monotherapy was used for 26 patients; the others were taking an average of two additional antiepileptic drugs. The average daily dose of LEV was 2208 mg. Pyridoxine was started at 50 mg/day, and if no or partial benefit was noted, the dose was increased to 100 mg/day. However, the average dose to control the behavioral symptoms in our study was 54.5 mg/day (SD = 18.2). Most patients had reported behavioral problems within the first weeks after the addition of LEV. None of our patients, however, had preexisting behavioral issues prior to the use of LEV. None of the patients who did not receive pyridoxine supplementation reported any significant improvement in behavioral symptoms throughout the course of treatment with LEV. On average, the effects

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of pyridoxine supplementation were reported during the first 2 weeks. On a separate note, none of the patients who received pyridoxine supplementation reported any significant improvement in seizure frequency throughout the course of treatment with LEV.

#### 4. Discussion

To our knowledge, this is the first study that suggests a possible benefit 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 to control the LEV-induced behavioral symptoms. Miller [7] was able to control the behavioral disturbances caused by LEV completely, in 5 of 6 children aged between 2 and 10 years, by supplementing pyridoxine at an average dose of 7 mg/kg/day. In another study to examine the use of pyridoxine, Major et al. [8] analyzed 42 pediatric patients who had been treated with LEV and pyridoxine. Twenty-two patients started pyridoxine after being on LEV, due to behavioral side effects, and significant behavioral improvement was observed in nine (41%), no effect in eight (36%), deterioration in four (18%), and an uncertain effect in one. The effects of pyridoxine supplementation, similar to our study, were observed during the first week of its introduction.

Our study used a retrospective, chart review method and lacked a placebo-controlled approach. Our results demonstrated that 66% of patients who started pyridoxine after being on LEV had a significant behavioral improvement, and in the remaining one-third, pyridoxine was not helpful in preventing LEV-related behavioral side effects. Interestingly, and similar to previous reports in pediatric populations, the improvement occurred during the first few weeks after pyridoxine supplementation, probably supporting its potential effect.

Pyridoxine is a water-soluble cofactor in more than 100 enzyme-catalyzed reactions in the body, including many involved in the synthesis or catabolism of neurotransmitters. There is no known pharmacokinetic or pharmacodynamic interaction between LEV and pyridoxine that could explain its potential clinical benefit. On that note, it can be said that the underlying mechanism(s) that would explain its efficacy in controlling the behavioral adverse effects of LEV is largely unknown, and its recommended use to control these symptoms is empirical at best. Similarly, pyridoxine, based on empirical grounds, has been used to treat other medical conditions such as premenstrual depression [9]. On the other hand, pyridoxine has been tried based on our current understanding for 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) [10].

The average dose to control the behavioral symptoms in our study was less than 100 mg/day. This dose is considered quite safe. Toxicity of this supplementation tends to occur at a dose higher than 1000 mg/day [11,12]. Our study recommended doses much lower than the toxic threshold. Indeed, none of our patients had signs of toxicity, including neuropathy.

We realize the limitation of our study, being retrospective and from a single center. However, this preliminary study suggests that pyridoxine might be used safely to control LEV-induced behavioral side effects in adults. Whether vitamin B6 has the same efficacy in controlling behavioral symptoms in patients with epilepsy in general or it shows the same efficacy in those patients who are treated with other AEDs remains to be carefully examined. A prospective, placebo-controlled study is needed to confirm our finding and to address these unanswered questions.

#### Conflict of interest

All the authors declare no conflict of interest

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