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Brief Communication

Vitamin B6 decreases the risk of levetiracetam discontinuation in children with epilepsy: A retrospective study

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ABSTRACT

Objectives: Levetiracetam (LEV) is an anti-seizure medication (ASM) known to have significant behavioral side effects in children with epilepsy. These side effects may be improved by supplemental vitamin B6 (pyridoxine) use. Our research aimed to study risk factors for LEV side effects and the role of vitamin B6 in altering this risk.

Methods: We retrospectively analyzed the demographic and clinical profile of all pediatric patients on LEV treatment between July 2019 and December 2020. *T*-tests, Chi-square and Fisher exact tests were used to assess predictors of LEV discontinuation. A *p*-value of <0.05 was considered statistically significant.

Results: 150/240 (62%) children were on additional medications besides LEV for epilepsy management. Thirty-five percent children reported side effects, especially behavioral and mood concerns.

Of the patients who reported side effects on LEV, 71% were taking vitamin B6 ($n = 59$). The rate of LEV discontinuation was significantly lower for children on vitamin B6 than children not taking B6, regardless of monotherapy or polypharmacy (49% v 88% respectively, $p = 0.001$). Over half of the patients who were able to remain on LEV reported improved behavior with B6 supplementation as compared to those who were unable to continue LEV (17/30, 57% versus 0/26, 0%; $p < 0.001$).

Conclusions: Levetiracetam side effects significantly impact the tolerability of this ASM in children with epilepsy. Our results suggest that vitamin B6 supplementation can significantly reduce the odds of discontinuing LEV due to its behavioral side effects.

1. Introduction

Levetiracetam (LEV) is an anti-seizure medication (ASM) commonly used to treat epilepsy in children and adults. It is one of the most commonly prescribed ASMs worldwide for several reasons, including fast oral absorption, few interactions with other medications, and broad clinical efficacy against both focal and generalized seizures [1,2]. However, LEV is known for causing significant behavioral and mood side effects such as aggression, irritability, depression and worsening of existing behaviors, which can lead to discontinuation of medication [3,4]. Rates of general behavioral problems associated with LEV have been reported at up to 22% for adults and children [5,6]. Other commonly reported side effects include drowsiness, fatigue, headache, vomiting, and GI upset [2].

There is a growing body of literature suggesting that initiation of vitamin B6 (pyridoxine) helps reduce these behavioral side effects, although precise mechanisms of effect are incompletely understood [7,8]. Pyridoxal phosphate, the active form of B6, is a cofactor involved in the synthesis and breakdown of neurotransmitters including dopamine, glutamate, and GABA. An altered homeostasis of these neurotransmitters may contribute to cognitive/behavioral dysfunction. Therefore, it is hypothesized that supplementing with B6 may help replace low levels or overcome an increased B6 requirement [9,10]. However, data on the role of vitamin B6 in protecting patients from discontinuing LEV are lacking.

Our research aimed to study demographic and clinical risk factors for LEV discontinuation and assess the role of vitamin B6 in

Abbreviations: LEV, Levetiracetam; ASM, anti-seizure medication.

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modifying this risk. We hypothesized that children on vitamin B6 would have a lower likelihood of experiencing side effects from LEV and therefore increase tolerability.

2. Material and methods

We conducted a single center retrospective chart review of 240 children with epilepsy treated with LEV by the epileptologists at Hasbro Children's Hospital/Brown University who were followed up between July 2019 and December 2020. Inclusion criteria were age <18 years, a diagnosis of epilepsy based on the current International League Against Epilepsy (ILAE) definition, and treatment with LEV.

Data obtained from the electronic medical record included demographic data (age, sex, race, ethnicity), other medical diagnoses/comorbidities, detailed epilepsy history, including age of onset, epilepsy type and duration, frequency of seizures, and additional nonpharmacological treatments for epilepsy such as neurostimulation devices, dietary treatment, or epilepsy surgery. We also collected brain MRI results, electroencephalogram (EEG) results, family history of epilepsy, LEV dose, duration and associated side effects, vitamin B6 use and duration, and other ASMs used. All data collected were de-identified and stored in a password protected REDCap database. The study was approved by Rhode Island Hospital Institutional Review Board and certified exempt from obtaining consent.

For the purpose of data collection and analysis, we classified LEV side effects into five main categories – behavioral, mentation, mood concerns, disturbed sleep, and other, based on previous studies and the authors' clinical experience [11]. The behavioral side-effect category contained symptoms of restlessness, aggression, nervousness/agitation, irritability, and behavioral side effects not otherwise specified. The mentation side-effect category included tiredness, sleepiness, difficulty concentrating, memory problems, and difficulty thinking clearly. Mood concerns consisted of depression, moodiness/emotionality, and self-injurious behavior/suicidal ideation.

To investigate the associations between LEV discontinuation and vitamin B6, *t*-tests, Chi-square and Fisher exact tests were used to assess predictors of LEV discontinuation. All analyses were performed using SAS release 9.4 (SAS Institute Inc.). A *p*-value of <0.05 was considered statistically significant.

3. Results

Table 1 shows the demographic and clinical characteristics of the 240 participants in this study. The only variable that significantly differed between patients was the duration of LEV use. As expected, patients who reported LEV side effects had a higher chance of discontinuing the medication within the first six 6 months of treatment whereas patients who did not report side effects remained on LEV for at least 12 months or more.

Over half of the children in this study (n = 150/240) were on additional medications besides LEV for epilepsy management, including oxcarbazepine (56/150; 37%), valproic acid (51/150; 34%), clobazam (36/150; 24%), topiramate (33/150; 22%), lamotrigine (30/150; 20%), zonisamide (29/150; 19%), phenobarbital (27/150; 18%), ethosuximide (16/150; 11%), lacosamide (12/150; 8%), rufinamide (9/150; 6%), cannabidiol (5/150; 3%), phenytoin (3/150; 2%), and carbamazepine (1/150; 1%). Eighty-three patients (35% of the sample) reported side effects while taking LEV alone or with other ASMs. Behavioral and mood concerns were the most frequently endorsed side effects, reported at 50% and 24%, respectively. Twelve percent of side effects were related to mentation, 5% were due to sleep disturbance, and the remaining 9% were due to other causes. The rate of side effects among children on polypharmacy was 41.3% (n = 62) as compared to 23% among children on LEV monotherapy (n = 21).

Of the patients who reported side effects on LEV, 71% were taking vitamin B6 (n = 59). Twenty patients with mostly pre-existing behavioral concerns (e.g. autism spectrum disorder, attention-deficit/hyperactivity disorder) were started on LEV and B6 concurrently. For the remaining 39 patients who were started on B6 after LEV, the most common reasons for B6 initiation were aggression, irritability, and moodiness. Table 2 and Fig. 1 illustrate the relationship between vitamin B6 use and discontinuation of LEV. The rate of LEV discontinuation was significantly lower for children on vitamin B6 than children not taking vitamin B6, regardless of monotherapy or polypharmacy (49% v 88%, respectively, p = 0.001). The dose of vitamin B6 and the time at which vitamin B6 was initiated had no significant impact on the odds of discontinuing LEV. Over half of the patients who were able to remain on LEV reported improved behavior with B6 supplementation as compared to those who were unable to continue LEV (17/30, 57% versus 0/26, 0%; p < 0.001).

4. Discussion

In this study, we found that the rate of LEV discontinuation was significantly lower in children who were taking supplemental vitamin B6 compared to those not taking it (n = 29/59; 49% versus n = 21/24; 88% respectively). No demographic or clinical variable showed an effect on the discontinuation rate.

Of the five categories of side effects we studied, behavioral and mood side effects predominated. This finding corresponds with multiple previously published papers [6,12]. In a retrospective study of 351 children treated with LEV between 2005 and 2015, the most commonly reported side effects were irritability, hyperactivity, and behavioral disorders, all of which would fit into this study's behavioral side effects category [12]. Therefore, it is conceivable that the behavioral side effects are the leading cause of LEV discontinuation.

In the current study, discontinuation of LEV occurred within the first six months of treatment. A review on the efficacy, tolerability, and safety of LEV in children with epilepsy supports this finding, stating that changes in behavior usually occur early during treatment [13].

The rate of behavioral side effects was higher in patients on polytherapy versus monotherapy, suggesting an unwanted synergy in causing side effects despite no drug–drug interactions of LEV with other ASMs. Our finding is consistent with a systematic review of adverse events related to LEV use, which found that significantly more children on polytherapy including LEV experienced side effects versus those on LEV monotherapy (64% v 22%, p < 0.001) [14]. Additionally, more children on polytherapy discontinued LEV than those on monotherapy. In both groups, the major contributing factor to discontinuation was behavioral problems. In future prospective studies, we hope to investigate which of other ASMs may increase the risk of behavioral side effects reported while on LEV.

In our cohort, the rate of LEV discontinuation was significantly lower in children who were taking vitamin B6, regardless of the timing of vitamin B6 initiation. This finding supplements previous research reporting that vitamin B6 helps reduce behavioral side effects resulting from LEV [15]. Furthermore, our data have shown that vitamin B6 can effectively increase the overall LEV tolerability in pediatric patients and therefore make the treatment more sustainable. Because of its retrospective nature, this study cannot address whether an earlier initiation of vitamin B6 or concurrent initiation of LEV and vitamin B6 is more effective in reducing the

Table 1
Demographic and clinical characteristics of study cohort.

Variable		No LEV side effect (*N* = 157)	LEV side effect (*N* = 83)	*P* Value
Sex (*n*, %)	Female	71 (45.22)	34 (40.96)	0.53
	Male	86 (54.78)	49 (59.04)	
Race (*n*, %)	White	78 (49.68)	53 (63.86)	0.07
	Black	21 (13.38)	11 (13.25)	
	Other	58 (36.94)	19 (22.89)	
Ethnicity (*n*, %)	Not Hispanic	107 (68.59)	64 (77.11)	0.16
	Hispanic	49 (31.41)	19 (22.89)	
Age at Last Follow-Up (months)	Median (Interquartile)	118.00 (58.00–168.00)	117.00 (60.00–168.00)	0.92
Age of Seizure Onset, (months)	Median (Interquartile)	36.00 (9.00–84.00)	36.00 (12.00–72.00)	0.67
Type of Seizure (*n*, %)	Focal	84 (53.50)	48 (57.83)	0.39
	Generalized	43 (27.39)	25 (30.12)	
	Multi-focal	1 (0.64)	0 (0)	
	Both generalized and focal features	3 (1.91)	3 (3.61)	
	Unknown	26 (16.56)	7 (8.43)	
MRI Results (*n*, %)	None (not completed)	24 (15.29)	10 (12.05)	0.43
	Normal	63 (40.13)	41 (49.40)	
	Seizure focus	27 (17.20)	14 (16.87)	
	Incidental	39 (24.84)	18 (21.69)	
	Tumor	4 (2.55)	0 (0)	
Levetiracetam Duration (*n*, %)	Less than 6 months	13 (8.28)	30 (36.14)	**< 0.001**
	6–12 months	23 (14.65)	9 (10.84)	
	12 months or more	113 (71.97)	37 (44.58)	
	Unknown	8 (5.10)	7 (8.43)	
Levetiracetam Dose (mg/kg/day)	Median (Interquartile Range)	38.00 (27.00–54.00)	33.00 (22.00–44.00)	0.08

Table 2
Analysis of 83/240 (35%) children on LEV who reported side effects.

Variable		LEV discontinued (*N* = 50)	LEV not discontinued (*N* = 33)	*P* values
Has participant ever taken B6? (*n*, %)	Yes	29 (49.15; 29/59)	30 (50.84; 30/59)	**0.001**
	No	21 (87.5; 21/24)	3 (12.5; 3/24)	
B6 dose (mg/kg/day)	Median (Interquartile Range)	3.20 (2.30–4.20)	3.50 (2.00–5.10)	0.59
Was B6 started at the same time as LEV? (*n*, %)	Yes	13 (44.83)	7 (23.33)	0.08
	No	16 (55.17)	23 (76.67)	
How many months after starting LEV was B6 added? (months)	Median (Interquartile Range)	1.00 (0.50–6.00)	2.88 (1.25–11.00)	0.32
Did behavior improve with B6? (*n*, %)	Yes	0 (0)	17 (56.67)	**< 0.001**
	No	26 (89.66)	5 (16.67)	
	Unknown	3 (10.34)	8 (26.67)	

odds of discontinuing LEV. A prospective cohort study will be more suited for this question.

A recently completed randomized controlled trial showed that vitamin B6 doses of 0.5 mg/kg/day and 10–15 mg/kg/day were both associated with significant reductions in LEV-related behavioral effects, but no additional doses were evaluated [16]. All patients in this trial were started on LEV and vitamin B6 concurrently, which may not reflect real-life practice. In our study, we found that most of our patients had started vitamin B6 after LEV-related side effects were suspected. Future studies can be designed to assess the efficacy of early versus late initiation of vitamin B6 to mitigate LEV-related side effects. If early supplementation shows superiority, it may not be unreasonable to design a novel LEV formulation which includes vitamin B6.

In our analysis the average vitamin B6 dose was similar in the subset of children who continued LEV versus those who had stopped it (3.50 mg/kg/day vs. 3.20 mg/kg/day, respectively). Analyzing dose-dependency for supplemental vitamin B6 and LEV discontinuation is another question for future prospective studies.

This study has limitations. The first is that the retrospective design limited the data collected on each participant, including missing information in the medical record for study-specific variables, particularly LEV dose, vitamin B6 dose, and the impact of vitamin B6 on behavior. Sixteen patients did not have a LEV dose reported (16/240; 7%), 10 were missing a vitamin B6 dose (10/59; 17%) and 11 did not report whether vitamin B6 improved behavior (11/59; 19%). The second is the potential recall bias that is introduced from parent-reported side effects. Epilepsy management in over half of the cohort consisted of polypharmacy, which could lead to misattribution of side effects from a different ASM to LEV. The third is that we did not have a baseline and follow-up formal neuropsychological profile on study participants. This notion is relevant in the context of ASMs since underlying behavioral disturbances, such as baseline hyperactivity levels, have been associated with more severe ASM behavior side effects, regardless of ASM used [17]. Moreover, LEV may promote depression or anxiety symptoms especially among children with underlying mood or anxiety disorders [18].

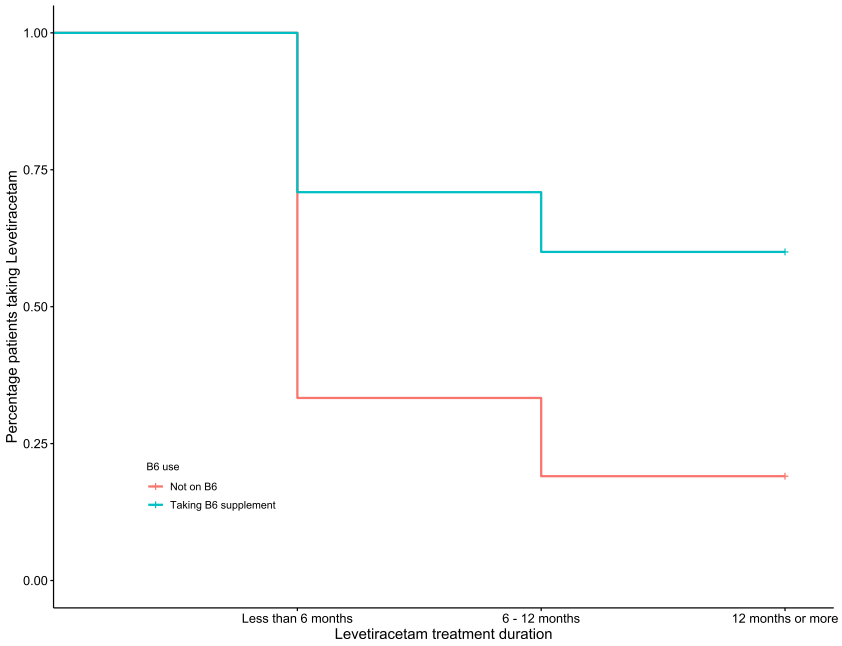

Fig. 1. Kaplan–Meier curve estimating the odds of not discontinuing levetiracetam when receiving supplemental vitamin B6.

5. Conclusions

We found that rates of LEV discontinuation were lower in children who were taking vitamin B6, regardless of monotherapy or polytherapy, suggesting that pyridoxine supplementation can significantly reduce the odds of discontinuing LEV due to its side effects. As further research on the dosing and timing of vitamin B6 initiation emerges, clinicians may be encouraged to either try B6 supplementation prior to switching to a different ASM or proactively providing B6 supplementation in conjunction with LEV.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2022.108839.

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