



Levetiracetam-associated irritability and potential role of vitamin B6 use in veterans with epilepsy



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ABSTRACT

Objectives: Levetiracetam, a commonly prescribed antiseizure medication (ASM), may cause irritability, depression, and anger. The mechanisms underlying these behavioral effects and individual risk factors remain unknown. Mitigation strategies are limited, including discontinuation, supplementation with vitamin B6, or switching to an alternative ASM. Several retrospective studies and anecdotal reports, primarily in pediatric populations, suggest vitamin B6 supplementation may be helpful in reducing levetiracetam-associated irritability. Although data in adult patients is limited, and no data is available for Veterans. The objective of this project was to describe our preliminary experience with vitamin B6 supplementation for alleviating levetiracetam-associated irritability in male Veterans with epilepsy. **Methods:** Retrospective chart reviews were completed for patients who had an active prescription for levetiracetam from the William S. Middleton Memorial Veterans Hospital from January 1, 2015 to June 1, 2020. A total of 26 charts were screened. Patients were excluded if not using vitamin B6 supplementation or if deceased at end of data collection. Baseline characteristics were compared, including age, sex, comorbidities, and concomitant medications. Charts were then reviewed to identify any clinical description of irritability, including subjective assessment of change in symptoms across multiple visits, and scores from standardized instruments including the patient health questionnaire (PHQ-9), generalized anxiety disorder questionnaire (GAD-7), and/or irritability in adult patients with epilepsy (I-EPI) questionnaire. These symptoms and scores were then compared pre- and post-B6 supplementation.

Results: Of 22 patients, data was available for 20 (91%). For patients with data available, 9 (45%) showed improved irritability following supplementation with vitamin B6 and 11 (55%) showed no improvement. **Conclusions:** This project suggests that vitamin B6 supplementation may have a role in mitigating levetiracetam-associated irritability in a male Veteran population. These results support future prospective controlled studies to assess further the efficacy of this approach and characteristics associated with successful treatment in veterans.

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1. Introduction

Levetiracetam, a synaptic vesicle protein 2A (SV2A) modulator, is a widely prescribed antiseizure medication (ASM) and especially useful in combination therapy or in patients with other comorbidities due to its limited risk of drug interactions [1]. Levetiracetam may be initiated at a therapeutic dose and is generally well toler-

ated. However, use of levetiracetam may be limited by behavioral adverse effects, most notably irritability, and less commonly depression, anxiety, and anger [2,3]. In clinical studies of individuals with focal-onset seizures, levetiracetam caused behavioral symptoms in 13.3% of patients compared to 6.2% in placebo-treated patients, while for genetic generalized epilepsy irritability was reported at rates as high as 6.3% compared to 2.4% of placebo-treated patients [2]. In veterans these adverse effects are of particular concern as 25% of veterans have at least one diagnosed mental health condition including depression, posttraumatic stress disorder, substance use disorder, anxiety, schizophrenia, or bipolar disorder [4].

Abbreviations: ASM, antiseizure medication; SV2A, synaptic vesicle protein 2A; GABA, gamma aminobutyric acid; 5-HT, serotonin; PLP, pyridoxal phosphate.

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Several retrospective studies and anecdotal reports, almost exclusively in children, suggest that vitamin B6 supplementation may be helpful in reducing or reversing the irritability that often occurs with levetiracetam [5]. Notably, there is a paucity of data in the older with epilepsy. While the mechanism(s) underlying behavioral adverse effects and irritability associated with ASMs, including levetiracetam, are not well understood, hypotheses include antagonism of the AMPA receptor, as well as GABA and 5-HT involvement [6]. However, despite the evidence for efficacy, it is unclear how vitamin B6 may interact with levetiracetam or one of these mechanisms to treat irritability.

Given the complicating features of the veteran population and the lack of data regarding treatment of levetiracetam-associated irritability in the adult population, we examined irritability in veterans with epilepsy who were treated with levetiracetam, as well as efficacy of vitamin B6 supplementation to reduce irritability, from a single epilepsy clinic within the Veterans Health Administration.

2. Materials & methods

The William S. Middleton Memorial Veterans Hospital electronic medical record was searched to identify patients with both active levetiracetam and vitamin B6 prescriptions during the period from January 1, 2015 to June 1, 2020. Charts were reviewed for those patients with concomitant active prescriptions, looking exclusively at the records from epilepsy-specific visits and telephone encounters. Patients were excluded if they were deceased prior to the end of data collection, or if they were using over-the-counter vitamin B6, given the inability to confirm both the dose as well as adherence in an objective manner. Irritability was assessed until vitamin B6 was discontinued, levetiracetam was discontinued, or until it was unknown whether the patient was still taking vitamin B6. Collected patient data include demographics, subjective irritability reports, and objective symptom assessment questionnaire scores (PHQ-9 and GAD-7) at baseline and each follow-up visit. Prescribed medications besides levetiracetam and pyridoxine were tracked during data collection with specifics including total medications at baseline, number and type of psychiatric medications at baseline, as well as number and type of ASMs prescribed. Comparisons were made among patients noting subjective improvement, those not endorsing subjective improvement and those with unknown effects of vitamin B6. Comorbid diagnoses were also documented with particular attention to mental health diagnoses. Subjective improvement was evaluated in all included patients. Objective improvement was evaluated only in patients with both baseline and final PHQ-9 and GAD-7 measurements available. As this was a pilot study, no statistical analyses were performed.

3. Results

Search of the electronic health records identified 465 active prescriptions for pyridoxine or levetiracetam from January 1, 2015 to June 1, 2020. These active prescriptions were for 297 unique patients, with 16 patients identified to have concomitant levetiracetam and pyridoxine prescriptions. Ten additional patients prescribed levetiracetam received a pyridoxine prescription for irritability during the data collection period and were included in analysis for a total of 26 patients. Four patients were excluded; three were deceased prior to the end of data collection and one was lost to follow-up. Baseline characteristics of the 22 included patients are outlined in table 1. The most commonly prescribed total daily dose of levetiracetam was 2000 mg (most often split into 1000 mg twice daily), and for vitamin B6 was 100 mg daily

Table 1
Baseline patient characteristics N = 22.

Age (years; median, range)	63.5 (36–93)
Male (%)	100
Race (%)	
-Caucasian	68
-African American	18
-American Indian or Alaskan Native	5
-Declined to Answer	9
Baseline PHQ-9 (median) (data available for 18 patients)	6.5
Baseline GAD-7 (median) (data available for 15 patients)	3
Patients with mental health diagnoses (%)	68
-Depression	40
-PTSD + Depression	20
-PTSD	13
-Anxiety + Depression	7
-PTSD + Depression + Anxiety	7
-Mood Disorder	7
-Adjustment Disorder	7

(most often dosed once daily). Of the 22 patients included, 9 had subjective improvement in irritability, while 11 did not show subjective improvement by the end of the data collection time frame. There were 2 patients for whom the effects of vitamin B6 were unknown. Of the 9 patients who endorsed subjective improvement, 6 of them had comorbid mental health diagnoses. Of the 11 patients who did not endorse subjective improvement, 7 of them had comorbid mental health diagnoses. Both patients in the unknown irritability category had comorbid mental health diagnoses. Table 2 summarizes patient characteristics among those who reported subjective improvement, those who did not report subjective improvement, and those for whom the effects of B6 remained unknown.

When interpreting data on objective improvement, baseline and final PHQ-9 and GAD-7 scores were available for 10 patients. For the remaining 12 patients either baseline PHQ-9/GAD-7 or final PHQ-9/GAD-7 were unavailable. Table 3 shows the median baseline and final scores from both PHQ-9 and GAD-7 objective assessments for the 10 patients in whom this data is available.

Subjective improvement was compared to change in objective scores from baseline to final in the 10 patients for whom objective scores were available. Of those 10, 4 had subjective improvement and changes in their objective scores are as follows: one patient had no changes in objective scores, another patient had worsening of their PHQ-9 but improvement in the GAD-7, and the third and fourth patients improved in the PHQ-9 but remained the same in the GAD-7. Five of the 10 patients subjectively did not improve, and changes in their objective scores are as follows: one patient improved in both the PHQ-9 and GAD-7, another patient worsened in both assessments, a third patient improved in the PHQ-9 and worsened in the GAD-7, the fourth patient markedly improved in the PHQ-9 but remained the same in the GAD-7, and the last patient remained the same in both assessments. One patient had unknown subjective improvement but showed notable improvement in both measures.

Adverse effects from Vitamin B6 supplementation were not reported for any of our patients.

4. Discussion

We present our experience with levetiracetam-associated irritability and vitamin B6 supplementation in a cohort of male veterans with epilepsy. We identified 22 adults treated with levetiracetam and vitamin B6. Irritability was evaluated in 20 (91%) records, with improvement in irritability in 9 (45%) of those

Table 2
patient characteristics by subjective improvement *N* = 22.

	Subjective Improvement <i>N</i> = 9	No Subjective Improvement <i>N</i> = 11	Unknown Improvement <i>N</i> = 2
Age (years; median, range)	66 (39–73)	62 (36–93)	55 (46–64)
Race (number of patients)			
-Caucasian	6	8	1
-African American	1	2	1
-American Indian or Alaskan Native	0	1	0
-Declined to Answer	2	0	0
Baseline PHQ-9 (median)	5 (data available for 9 patients)	7 (data available for 7 patients)	7.5 (data available for 2 patients)
Baseline GAD-7 (median)	3 (data available for 7 patients)	3.5 (data available for 6 patients)	6.5 (data available for 2 patients)
Patients with Mental Health Diagnoses (number of patients)			
-Depression	5	4	2
-Anxiety	1	1	1
-PTSD	2	4	1
-Mood Disorder	0	1	0
-Adjustment Disorder	0	1	0
-Alcohol Dependence	1	2	2
-Insomnia	3	0	1
-Cognitive Disorder	0	0	1
-Simple Phobia	0	0	1
-Tobacco Use	2	1	1
-Opioid Dependence	0	1	0
-Cannabis Use	1	0	0
Psychiatric Medications at Baseline (average)	1.3	0.8	2
Psychiatric Medications Prescribed (number of patients)			
-Buspirone	1	0	0
-Citalopram	3	1	0
-Duloxetine	0	0	1
-Hydroxyzine	0	1	1
-Lorazepam	0	1	0
-Mirtazapine	2	1	1
-Prazosin	2	0	0
-Risperidone	0	1	0
-Sertraline	1	2	0
-Trazodone	1	1	0
-Venlafaxine	0	1	0
-Varenicline	0	0	1
Total Medications at Baseline (average)	10.2	9	19.5
Epilepsy Diagnosis (number of Patients)			
-Focal Epilepsy	2	5	2
-Post-Traumatic Epilepsy	3	0	0
-Post-Stroke Epilepsy	2	2	0
-Generalized Epilepsy	1	2	0
-Epilepsy of Unknown Etiology	0	2	0
-Epilepsy in Setting of Alzheimer's Dementia	1	0	0
Seizure Type (number of patients)			
-Focal with Impaired Awareness	3	0	1
-Focal without Impaired Awareness	1	0	0
-GTCs	1	3	0
-Focal with Impaired Awareness with Evolution to GTCs	2	5	1
-Focal without Impaired Awareness and GTCs	0	1	0
-Focal with Impaired Awareness and Nocturnal GTCs	0	1	0
-PNES and GTCs	1	0	0
-Focal (no further description)	1	1	0
Antiseizure Medications (average)	1.6	1.3	1
Patients on Levetiracetam Monotherapy (number of patients)	4	8	2
Patients on ASM Combination Regimens (number of patients)			
-Levetiracetam + Lacosamide	1	0	0
-Levetiracetam + Phenytoin	1	0	0
-Levetiracetam + Zonisamide	1	0	0
-Levetiracetam + Divalproex	1	3	0
-Levetiracetam + Lamotrigine	1	0	0

veterans. Data on pyridoxine use for levetiracetam-associated behavioral adverse effects is very limited outside of the pediatric population, and to our knowledge this is one of the few reports exclusively in adult and older adult patients with a median age

of 63.5 years. The efficacy of vitamin B6 supplementation to treat levetiracetam-associated irritability we present here is similar to that seen in younger adult populations (mean age 34.2 years old) [7].

Table 3
Change from baseline *N* = 10.

PHQ-9 (median)	
-Baseline	4
-End of data collection	2
GAD-7 (median)	
-Baseline	2.5
-End of data collection	2

Levetiracetam has many favorable characteristics leading to common use to treat seizures in veteran and civilian populations. However, the goal of treatment for epilepsy is freedom from both seizures and adverse effects. As levetiracetam-associated irritability is not infrequent, a common clinical conundrum is the patient treated with levetiracetam with good seizure control but significant irritability. This conundrum is more common and risks elevated in Veterans, given the high rate of comorbid mental health disorders in Veterans as well as an overrepresentation of Veterans in violent crimes [8]. Despite these potential difficulties with treatment of irritability in Veterans, we found that nearly half of veterans had improvement with vitamin B6 supplementation.

In terms of safety, vitamin B6 is generally well-tolerated, though doses much higher than those used in this study may lead to reversible sensory peripheral neuropathy, as seen in patients who had taken 2,000 – 6000 mg/day for 2–40 months [9]. Animal models suggest the risk of neuropathy significantly decreases with doses less than 1 g/day [9], also supporting the safety of the doses used for levetiracetam-associated irritability.

The mechanisms by which vitamin B6 improves levetiracetam-associated irritability is unknown. In normal physiology vitamin B6 is involved in protein metabolism, cognitive development, immune function, and hemoglobin formation [9]. Pyridoxal phosphate (PLP) is the biologically active, coenzymatic form of vitamin B6, and is crucial in the synthesis of neurotransmitters including norepinephrine, serotonin (5-HT), and GABA. Pyridoxine depletion or deficiency has been shown to decrease glutamic acid decarboxylase, glutamic acid, and 5-hydroxytryptophan (5-HT) concentrations in rodent models [10,11]. In humans, vitamin B6 deficiency (typical reference range for PLP is 5–50 ug/ml) can lead to anemia, depression, confusion, and immunosuppression, has been linked to irritability and seizures in infants [12], and implicated in status epilepticus [13].

In addition to the treatment of levetiracetam-associated irritability, supplementation of vitamin B6 has been studied in reducing the prevalence of tardive dyskinesia in patients with schizophrenia [14], reducing premenstrual syndrome symptoms including irritability, moodiness, and anxiety [12,15], as well as potentially leading to improvement of depression symptoms in elderly patients [12,16]. In animal models, vitamin B6 also prevented depression induced by dexamethasone [17]. These effects may be due to metabolic modulation of glutaminergic effects in the brain and/or diurnal cortisol secretion patterns.

As with all retrospective studies, there are limitations to this study. First, inconsistent documentation of both adverse effects as well as PHQ-9 and/or GAD-7 scores was noted for follow up appointments, though despite the retrospective nature of the study 91% of veterans treated with levetiracetam and vitamin B6 had data regarding irritability. Second, patient follow up visits were highly variable in timing, making it difficult to correlate treatment and response as well as to extrapolate at what time-intervals it would be appropriate to titrate B6 dosing. Third, variability between objective measurements and subjective patient report at the same visit made assessment of irritability improvement challenging, highlighting the limitations of our ability to assess this amorphous symptom. Variability in objective scores and the dis-

crepancies between objective measures and more narrative, subjective symptom is not unexpected, but highlights the need for standardized assessments for irritability in this population. While irritability is often seen in the context of mood and anxiety disorders, it is distinct in its presentation, characterized by increased sensitivity to triggers and an angry response of magnitude greater than the patient's baseline or what would be expected for a given situation. In the case of levetiracetam, irritability appears to be significantly more common than depressive mood or anxiety [3]. It is therefore unsurprising when PHQ-9 and GAD-7 scores do not necessarily correlate with subjective reports of irritability. Hence, the PHQ-9 and GAD-7 may not capture a patient's irritability symptoms in an accurate fashion. This may be important not only for patients on levetiracetam, but for the epilepsy population in general. Finally, pyridoxine blood concentrations were not available in this evaluation, to allow determination as to whether a vitamin B6 deficiency was associated with either adverse effects, or a positive therapeutic response to supplementation.

An important consideration and limitation in studying levetiracetam associated-irritability evident in our review of vitamin B6 is the presence of comorbid mental health conditions. Majority of the veterans (68%) who trialed vitamin B6 had comorbid mental health conditions, including most notably depression, anxiety and PTSD. Because psychiatric or behavioral side effects of ASMs are strongly predicted by a previous psychiatric or mental health history [18], the comorbid mental health conditions in these patients may have made them more likely to experience levetiracetam-associated irritability.

These mental health conditions also complicate irritability assessment. Especially at our institution, veterans with mental health concerns are closely followed by our mental health clinic, with frequent medication adjustments. Given that the behavioral side effects of levetiracetam can mimic and overlap with many symptoms of mental health comorbidities, it was difficult in our project to confirm if the changes in irritability are solely a result of vitamin B6 augmentation or mental health medication changes made during the same timeframe. However, it would severely limit the generalizability of our results if mental health patients were excluded.

Despite these limitations, vitamin B6 is an efficacious, low-cost, well-tolerated treatment in a subset of patients, suggesting a role in the management of levetiracetam-associated irritability in veterans.

5. Conclusions

To our knowledge, this is the first assessment of vitamin B6 use in levetiracetam-associated irritability exclusively in male veterans. Furthermore our data also underscores the need to develop and implement improved measurements of irritability, which may need to be tailored with respect to the population and the disease being assessed. The presented findings support future prospective, randomized, placebo-controlled studies to assess the use of vitamin B6 supplementation for levetiracetam-associated irritability.

Declaration of competing interest

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