

## Levetiracetam "Narrative Review of Neuropsychiatric Issues"

**Running Title:** Levetiracetam and Neuropsychiatry

**Reza Bidaki<sup>1,2</sup>, Habibollah Afshang<sup>3\*</sup>**

<sup>1</sup>Research Center of Addiction and Behavioral Sciences, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

<sup>2</sup>Diabetes Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

<sup>3</sup>Student Research Committee, Faculty of Pharmacy, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

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### Corresponding author

Student Research  
Committee, Faculty of  
Pharmacy, Shahid  
Sadoughi University of  
Medical Sciences, Yazd,  
Iran.

Tel: +98-3136825569

E-mail

[ali\\_alizadeh99@yahoo.com](mailto:ali_alizadeh99@yahoo.com)

### Abstract

#### Introduction

Levetiracetam, an anti-epileptic drug, is usually used as an adjunctive treatment of partial-onset seizures with or without secondary generalization. In this article, various neuropsychiatric effects of Levetiracetam are investigated.

#### Methods

The following databases were searched: PUBMED, Google Scholar, MEDLINE, Embase, ProQuest, and Science Direct. The articles searched in the mentioned databases were from 2003 to 2021. Ninety-nine articles were selected, fifteen articles such as case reports and letters to the editor were removed due to low scientific credibility, and eighty-four articles were selected. Due to the small number of articles, articles in the form of case reports and letters to the editor were also used to write about mania.

#### Results

Case reports showed that some cases of behavioral disorders, aggression, and depression had been observed following the use of Levetiracetam. In this study, various evidence were collected to determine the performance of Levetiracetam and to what extent it can have important and vital side effects. This drug can strengthen suicidal thoughts and aggression in consuming patients, especially the patients with other underlying diseases.

#### Conclusion

According to the side effects mentioned for Levetiracetam, it is suggested that psychiatrists and neurologists pay more attention to these side effects when prescribing.

**Keywords:** Levetiracetam, Anxiety, Cognition Disorders, Depression, Problem Behavior, Psychiatry, Suicide

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## **Introduction**

A second-generation anti-epileptic drug (AED) is Levetiracetam. This drug is usually used as an adjunctive treatment of partial-onset seizures with or without secondary generalization. Other uses include the adjunctive therapy of myoclonic seizures with juvenile myoclonic epilepsy and primary generalized tonic-clonic seizures (GTC) associated with generalized epilepsy, as well as the monotherapy of partial-onset seizures with or without secondary generalization (1). Levetiracetam is also approved as adjunctive therapy in adult patients with partial seizures.

In a trial conducted on adults with refractory partial seizures with or without secondary generalization, oral Levetiracetam was administered as an adjunctive medication for 18 weeks at daily doses of 1000, 2000, and 3000 mg, which showed that it significantly increased the response rate and reduced the frequency of seizures compared to placebo. Although Levetiracetam with a dose of 1000 and 2000 mg daily did not show much effect, Levetiracetam with a dose of 3000 mg daily significantly increased the number of seizure-free patients; it should be noted that the effects of seizure severity were not evaluated in these trials (2).

## **Methods**

The following databases were searched: PubMed, Google Scholar, MEDLINE, Embase, ProQuest, and Science Direct. The articles searched in the mentioned databases were from 2003 to 2021. Ninety-nine articles were selected, fifteen articles such as case reports and letters to the editor were

removed due to low scientific credibility, and eighty-four articles were selected. Due to the small number of articles, articles in the form of case reports and letters to the editor were also used to write about mania. The keywords used for the search were: "Levetiracetam", "agitation", "depression", "anxiety", "drowsiness", "mania", "aggression", "behavioral disturbance", "cognitive disorders", "suicide", and "Psychiatric complications".

## **Result**

### **Cognitive function and behavioral disturbance**

Studies of levetiracetam-induced behavioral and functional disorders found that patients with epilepsy treated with Levetiracetam had significantly more behavioral disorders than the patients with cognitive and anxiety disorders who did not use the drug (3). It should also be noted that although Levetiracetam has very positive and sound effects in the patients with epilepsy, physicians should also consider the negative effects of this drug on patients' cognitive function (4) In some cases, patients were forced to discontinue Levetiracetam due to behavioral disorders, such as irritability, anxiety, anger, restlessness, depression, mood swings, aggression, fatigue, and insomnia (**Table 1**) (5-9).

**Table 1.** Behavioral disturbance and cognitive function studies

Journal	Year of publication	Authors	Conclusion and Results	Number
Epilepsy & Behavior	2003	Joyce A Cramer et al	Increased behavioral disorders in patients treated with Levetiracetam	1
Seishin Shinkeigaku Zasshi	2012	Mitsutoshi Okazaki	Adverse effects of Levetiracetam on cognitive function of patients	2
Epilepsy & Behavior	2015	Stephen L Yates et al	Discontinuation of Levetiracetam due to behavioral disorders	3
John Libbey Eurotext	2016	Aldenkamp A, et al	Cognitive impairment of complications leads to the discontinuation of Levetiracetam.	4
Springer Nature	2017	Lagae L	Behavioral and Cognitive disorders caused by Levetiracetam	5
Brain Development	2017	Moavero R et al	behavioral and Cognitive disorders caused by Levetiracetam in children	6
Epilepsy & Behavior	2017	Chen B, Choi H, et al	Higher prevalence of behavioral and psychiatric side effects among anti-epileptic drugs with Levetiracetam	7

### Neuropsychiatric adverse events

Studies have shown that one out of the seven patients with epilepsy who have symptoms of psychosis increases their symptoms due to the use of anti-epileptic drugs such as Levetiracetam (10, 11). Although Levetiracetam is a suitable and effective drug for epilepsy and seizures, the psychiatric side effects of this drug should not be

ignored (12). because the seventy-seven percent of Levetiracetam users suffer from psychiatric side effects (13) the findings of a study strongly advise physicians to pay special attention to adverse drug reactions to anti-epileptic drugs such as levetiracetam, which may cause distressing conditions for patients (**Table 2**) (10-16).

**Table 2.** Neuropsychiatric adverse events studies

Journal	Year of publication	Authors	Conclusion and Results	Number
Epilepsia	2013	Helmstaedter C et al	High prevalence of psychiatric side effects with levetiracetam	8
Seizure	2016	Tekgöl H et al	Irritability, hyperactivity, and drowsiness are common side effects of levetiracetam.	9
Brain	2016	Chen Z et al	Increased symptoms of psychosis with levetiracetam	10
PLOS One	2018	Yang TW et al	Recommendation not to ignore the psychiatric side effects of levetiracetam	11

Epilepsy & Behavior	2019	Theochari E et al	Seventy-seven percent of Luriracetam users suffered from psychiatric side effects.	12
BMC Pharmacol Toxicol	2019	Du Y et al	Advise physicians to consider the adverse psychiatric side effects of Levetiracetam	13
Epilepsy & Behavior	2019	Foo EC et al	Discontinue Levetiracetam due to drowsiness, aggression, and depression	14

**Anxiety and depression**

Several studies on the psychiatric side effects of antiepileptic drugs such as Levetiracetam have shown that these drugs can cause depression, anxiety, and aggression, in order to these problems special attention should be paid to these side effects. Unfortunately, the patients with epilepsy are more prone to depression. Worse than that, the cause of this depression, and the

complications of epilepsy, can be due to the use of antiepileptic drugs such as Levetiracetam (17-19). It is noted that Levetiracetam is one of the best anti-epileptic drugs for treating epileptic patients. Still, one of the limitations of this drug is that it can cause behavioral disorders, especially depression treating epilepsy; it is better to pay special attention to the behavioral disorders caused by this drug in these patients (Table 3) (17-22).

*Table 3.* Anxiety and depression studies

Journal	Year of publication	Authors	Conclusion and Results	Number
JOHN LIBBEY EUROTEXT	2018	Dussaule C et al	There is a need to pay special attention to the psychiatric side effects of levetiracetam	15
Epilepsia	2012	Delanty N et al	Seventy-six percent of patients had emergency psychiatric complications with levetiracetam	16
Expert Review of Neurotherapeutics	2016	Tao K et al	Induction of depression by Levetiracetam in patients with epilepsy	17
Brain Research	2021	Hussain M, et al	Attention to behavioral disorders, especially depression, following the use of levetiracetam	18
Epilepsy & Behavior	2015	Mula M, et al	The use of Levetiracetam puts patients at seven times the risk of depression.	19

Neurochemistry International	2017	Singh T et al	Exacerbation of depression in patients with seizures taking Levetiracetam	20
Journal of Neuro-Oncology	2018	Knudsen-Baas KM et al	Increased anxiety following taking Levetiracetam	21

**Suicide issue**

According to these studies, physicians are advised to pay special attention to the association between psychiatric disorders and suicidal behaviors in elderly patients who treated with anti-epileptic drugs such as levetiracetam. The U.S. Food and Drug Administration has warned of increased

suicidal ideation and suicide attempts in the patients treated with anti-epileptic medicines such as levetiracetam. Unfortunately, there is a clinical correlation between suicidal behaviors and the patients with epilepsy. levetiracetam can increase suicidal behaviors in these patients (**Table 4**) (23-29).

*Table 4.* Characteristics studies about suicide issues

Journal	Year of publication	Authors	Conclusion and Results	Number
Journal of the American Geriatrics Society	2012	Pugh MJ, et al	Special attention should be paid to the relationship between psychiatric disorders and suicidal behaviors in the elderly taking levetiracetam	22
Harvard review of psychiatry	2014	Siamouli M, et al	Warning about the possibility of increased thoughts such as suicide in patients treated with levetiracetam	23
International Journal of Psychiatry in Clinical Practice	2015	Fountoulakis KN et al	Increased suicidal ideation following taking levetiracetam	24
Epilepsia	2015	Park SJ et al	The risk of suicide-related behaviors with Levetiracetam is much higher than with other anti-epileptic drugs.	25
Current Pharmaceutical Design	2017	Pisani LR et al	Levetiracetam is associated with suicidal ideation and even suicidal behaviors.	26
Neurology	2019	de Bruijn M et al	The link between suicide and the use of Levetiracetam	27

primary care companion for CNS disorders	2020	Esang M et al	Patients with a previous history of psychiatry and who have been prescribed Levetiracetam are more likely to develop suicidal thoughts and behaviors than patients without a history of psychiatry.	28
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**Mania**

Several rare case studies have reported a rare, but important complication of mania due to Levetiracetam in children, however, several reports of Levetiracetam being used specifically to treat mania. Although Levetiracetam is an antiepileptic drug with a unique mechanism of

action related to aggression, hostility, and psychosis, the cause of these behavioral effects with Levetiracetam remains unknown. Some studies have described the acute onset of mania following treatment with Levetiracetam in people with no previous history of mania or hypomania (**Table 5**) (30-36).

*Table 5.* Surveys about mania

Journal	Year of publication	Authors	Conclusion and Results	Number
Clinical Neuropharmacology	2019	Ekinci N et al	One of the rare and important side effects of Levetiracetam is mania.	36
Therapeutic Advances in Drug Safety	2019	Altınöz AE et al	In one patient, it was found that the patient had levetiracetam-induced bipolar disorder.	37
Klinik Psikofarmakoloji Bulteni- Bulletin of Clinical Psychopharmacology	2015	Ozcan H et al	levetiracetam-induced bipolar disorder	38
journal of clinical psychopharmacology	2019	Meyrel M et al	Severe mania is one of the most likely psychiatric side effects of levetiracetam.	39

**Drowsiness**

The results of several studies in children and adults, as well as a review study, showed that

drowsiness is one of the most common and perhaps the most common psychiatric side effects of Levetiracetam (**Table 6**) (37-39).

**Table 6.** Surveys about drowsiness

Journal	Year of publication	Authors	Conclusion and Results	Number
Epilepsia	2009	Piña-Garza JE et al	Drowsiness is the most commonly reported side effect of Levetiracetam in children under four with epilepsy.	29
Therapeutic Advances in Neurological Disorders	2019	Steinhoff BJ et al	Drowsiness is one of the most common side effects of Levetiracetam.	30
International Journal of Neuroscience	2014	Mbizvo GK et al	The most common side effect of levetiracetam is drowsiness.	31
Epilepsy Research	2019	Cao Y et al	One of the most common side effects of Levetiracetam is drowsiness.	32
European Journal of Drug Metabolism and Pharmacokinetics	2018	Wang M et al	The most common side effect of Levetiracetam in patients with epilepsy is drowsiness.	33
Brain and Nerve	2013	Nakamura H et al	The most common side effect of emergency treatment with Levetiracetam is drowsiness.	34
Cochrane Database of Systematic Reviews	2017	Nevitt SJ et al	One of the most common side effects of Levetiracetam is drowsiness.	35

### Discussion

Studies related to behavioral and functional disorders caused using Levetiracetam indicated that the patients with epilepsy treated with Levetiracetam have shown significantly more behavioral disorders than the patients with the

same disease who have not used it (3). It should also be noted that although Levetiracetam has very positive and good effects in the patients with epilepsy, physicians should also consider the negative effects of this drug on patients' cognitive function (4). Even in some cases, some patients were forced to discontinue Levetiracetam due to

behavioral disorders, and brivaracetam was an alternative. The symptoms of behavioral disorders include irritability, anxiety, anger, restlessness, depression, mood swings, aggression, fatigue, and insomnia (5-9). Studies have shown that one out of seven patients with epilepsy who had symptoms of psychosis increased their symptoms due to the use of anti-epileptic drugs such as Levetiracetam (10). Although Levetiracetam is a suitable and effective drug for epilepsy and seizures, the psychiatric side effects of this drug should not be ignored (11) seventy-seven percent of Levetiracetam users suffer from psychiatric side effects (12). The findings of a study strongly advise physicians to pay special attention to adverse drug reactions to antiepileptic drugs such as levetiracetam, which may cause distressing conditions for patients (10-16). Due the effects of anti-epileptic drugs such as Levetiracetam to induce depression, anxiety, and aggression, due special attention should be paid to these patients. (19). It is noted that Levetiracetam is one of the best antiepileptic drugs for treating epileptic patients. Still, one of the limitations of this drug is behavioral disorders, especially depression, so doctors should pay much attention to positive and promising effects. In treating epilepsy, it is better to pay special attention to the behavioral disorders caused by this drug in patients (17-22). According to these studies, physicians are advised to pay special attention to the association between psychiatric disorders and suicidal behaviors in elderly patients who are treated with antiepileptic drugs such as Levetiracetam. The U.S. Food and Drug Administration has warned about increased suicidal ideation and suicide attempts in the

patients treated with antiepileptic drugs such as Levetiracetam. Unfortunately, there is a clinical correlation between suicidal behaviors and the patients with epilepsy. For the patients with epilepsy, one of the prescribed anti-epileptic drugs is Levetiracetam, which itself can increase suicidal behaviors in these patients (23-29). The results of several studies in children and adults, as well as a review study, showed that drowsiness is one of the most common and perhaps the most common psychiatric side effects of Levetiracetam (30-36). Several rare case studies have reported a rare, but essential complication of mania due to Levetiracetam in children and adults (37-39).

### *Conclusion*

According to the results of previous studies, it was found that behavioral disorders and suicidal ideation, some psychiatric complications, and drowsiness are common side effects of Levetiracetam. It should be noted that anxiety, aggression, and cognitive disorders are relatively common compared to the complications mentioned above and agitation is much less common than all the mentioned complications. On the other hand, Levetiracetam is used as an adjunct therapy in mania.

Therefore, psychiatrists and neurologists are advised to pay attention to these critical complications when prescribing this drug or to prescribe less if desired, or for the patients with these disorders such as depression, suicidal ideation, aggression, and other cases that are mentioned in detail, do not prescribe this drug.



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