The differential effect of levetiracetam on memory and anxiety in rats

Ewa Zwierzynska*, Bogusława Pietrzak

Department of Pharmacodynamics, Medical University of Łódź, Muszyńskiego 1, 90-151 Łódź, Poland

**Abstract**

Objective: One of the newest antiseizure medication is levetiracetam (LEV). It might be effective in various indications, not only related to convulsions. Central nervous system disorders are common during anticonvulsant therapy. The aim of this study was to assess the effect of LEV on various types of memory and anxiety in rats.

Methods: Adult male Wistar rats (n = 58) were given LV p.o. as a single (100 mg/kg or 500 mg/kg) or repeated doses (300 mg/kg). The effect of the drug on memory was assessed in the Morris water maze (MWM) (spatial memory), the passive avoidance (PA) (emotional memory) and the novel object recognition (NOR) (recognition memory). The anxiety was evaluated in the elevated plus maze (EPM).

Results: LEV administered as repeated doses disturbed the long-term recognition memory in NOR and locomotor activity in EPM. A single dose affected emotional memory in PA. LEV did not alter spatial memory in MWM.

Conclusions: LEV may cause memory and locomotor disturbances, but some of these adverse effects seem to be temporary and limited to the effect of acute dose.

© 2022 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Introduction

The new generation of antiseizure medications is a diverse group also used outside its epilepsy indications. One such drug is levetiracetam, which is not only structurally different from most known antiseizure medication, but also has a distinctive mechanism of action. The drug binds with the synaptic vesicle protein SV2A, a membrane protein present widely in the CNS and endocrine cells [1]. It also acts by inhibiting various types of voltage-activated Ca2+ channels [2–4]. Currently, the drug is approved in the therapy of various types of epileptic seizures but studies are ongoing to assess its effectiveness in the treatment of other neurological diseases. Some clinical studies suggest that the drug may be an effective adjunctive treatment for patients with anxiety disorders [5–6]. Furthermore, one of these future indications might be also memory deficits associated with Alzheimer’s disease. The results from a limited number of preclinical [7–8] and clinical studies [9] indicate that the drug may have beneficial effects on memory impairment. The other disease related to memory disturbance is alcohol addiction. It is well known that chronic ethanol has a negative effect on different structures of the CNS and disturb synaptic function and neuroplasticity [10]. Clinical trial results indicate that levetiracetam, unlike other new antiseizure medica-

tions, allows abstinence to be maintained without any influence on memory or verbal fluency [11]. Moreover, memory loss may also occur in patients with epilepsy [12] and some anticonvulsant drugs may elicit cognitive deficits. Among the new generation of drugs, topiramate appears to be particularly prone to these unfavorable effects. It seems that levetiracetam has a favorable safety profile and causes less neurocognitive side effects than topiramate [13].

Hence, the aim of this study was to assess the effect of levetiracetam on various types of memory and anxiety in rats. The spatial memory was evaluated in the Morris water maze (MWM) while the emotional memory associated with fear was assessed in the passive avoidance test (PA). The novel object recognition test (NOR) was used to investigate the short- and long-term recognition memory and the anxiety level was assessed in the elevated plus maze test (EPM).

2. Materials and methods

2.1. Animals

Forty-six adult male Wistar rats, weighing 230–260 g (approximately 14 weeks old), were obtained from the Mossakowski Institute of Experimental and Clinical Medicine (Warsaw, Poland). The rats were divided into three groups in MWM and PA tests (n = 10): LV-low dose, LV-high dose, and control group. The animals from
control and low-dose groups also participated in a repeated dose study. In the NOR and EPM tests, the rats were divided into two groups: LV (repeated doses) and control (n = 8).

The rats were housed in groups of four or five in plastic cages at a constant room temperature (20–22 °C) and in a 12-h light/12-h dark cycle. The rats from all groups had free access to water and the same food. Experiments were carried out between 8:00 a.m. and 4:00 p.m. The study was performed in accordance with European Union Directive 2010/63/EU and Polish governmental regulations concerning experiments on animals (Dz.U.05.33.289). All experimental protocols were approved by the Local Ethics Committee for Experimentation on Animals (resolutions no. 66/L B/121/2018; 9/LB231/2022).

2.2. Drug

Levetiracetam (Trund®, 10 mg/ml solution; Glenmark Pharmaceuticals) was administered directly to the stomach via an oral gavage. Levetiracetam (LEV) has a favorable pharmacokinetic profile. The drug is rapidly and almost completely absorbed after oral administration in rats. Plasma maximum concentration is observed about 1 h after single oral administration of LEV (54 mg/kg) in male rats [14] and food does not alter the pharmacokinetics of LEV [15].

In our study, a single dose of 100 mg/kg or 500 mg/kg was given about 1.5 h before the trial to assess the acute effect on memory processes. To study the effect of prolonged administration, the drug was administered repeatedly once a day at a dose of 300 mg for 14 (MWM, PA) or 21 days (NOR, EPM). The timeline of experiment procedures is shown in Fig. 1. In tests lasting several days (MWM, PA, NOR), the rodents received the drug after the end of the experiment procedures in order to avoid the impact of the acute dose on the results. The control group received a 1% aqueous solution of methylcellulose (0.2 ml/100 g).

2.3. Morris water maze test (MWM)

The MWM is a test used to assess spatial learning and memory [16]. It was performed in a circular pool (180 cm in diameter; 50 cm high walls) filled with water (22–24 °C) which was placed in a room with several visual cues used for navigation by the animal. The pool was virtually divided into four sections. A transparent circular platform (8 cm in diameter) was placed in the center of a selected quadrant about 2 cm below the surface of water; this was invisible to the swimming animals. The experiments were recorded with a camera which was hung above the pool allowing the test to be monitored in real time without eye contact between the animal and the researcher. Rat movement and entrance to the platform were tracked using ANY-maze software (ANY-maze, USA).

Initially, the animals were pre-trained to learn the experiment scheme during three days with the platform placed in a selected quadrant. Each trial started with the rat being placed in a different quadrant, facing the wall and was allowed to swim for 60 s. If the rat managed to find the platform, it stayed on it for 15 s to observe the environment. The animal failed to find the platform, it was placed there manually by the experimenter and permitted to stay on it for 15 s. The experiment was repeated for each animal four times per day with a 60-s interval between trials. The undisturbed learning process is indicated by shorter search time and swimming distance as well as longer time in the proper zone with platform in the following days of the study. After three-day pre-training, the retention test was performed using an analogous scheme but without the hidden platform. During this trial, the animal swam primarily in the quadrant that previously contained the platform; as it could not locate the platform in the previous place, the rat started to search for it along the entire pool. On the fifth day of the experiment, the rats were divided into three groups (control, LV-low dose, and LEV-high dose). The platform was moved to another quadrant and the activities of days 1–4 were repeated. The animals from control and LV-low dose groups that were used in the earlier stage (acute dose study phase) were included in the evaluation of the effect of multiple doses.

2.4. Passive avoidance test (PA)

The PA assesses emotional memory associated with fear and is based on the natural desire of a rodent to remain in dark places [17]. During the experiment, the rodents learn to avoid a selected compartment with an aversive stimulus. The PA was performed in a step-through, light–dark apparatus (Gemini Avoidance System, San Diego, USA) consisting of two compartments (25 × 20 × 17 cm) separated by a movable gate.

The first day of test (acquisition trial), consisted of a single trial. The animal was placed in the dark compartment and allowed to freely explore it during a 60-s habituation. Subsequently, the light was turned on and the gate was opened simultaneously. The ani-

---

**Fig. 1.** The timeline of experiment procedures. A) – first phase and B) – second phase of the study. LV – levetiracetam, MWM – Morris water maze test, PA – Passive avoidance test, EPM – Elevated plus maze test, NOR – Novel object recognition test. The solid line shows the tests performed before drug administration; the dotted line – after acute doses; the dashed line – after repeated doses. The rodents received acute dose of LV before test and repeated dose after the end of the test.
mal should move to the dark compartment due to a preference for dark places. When the rat completely entered into the dark compartment, the gate automatically closed and an electric foot shock (0.5 mA) was delivered for 3 s through the floor grid. Then the animal was held in the dark compartment for approximately 15 s to associate an aversive stimulus with the environment. The apparatus was cleaned with 70% isopropyl alcohol between trials.

The retention trial was performed 24 after the acquisition trial. The rats were subjected to similar but shock-free trial (max. 300 s). The step-through latency to the dark compartment was measured. The longer step-through latency reflects an undisturbed memory of the aversive stimulus.

2.5. Novel object recognition test (NOR)

The NOR is used to assess recognition memory and learning in rodents and it was performed as described previously [18]. The test consisted of three phases – habituation, familiarization, and testing. On the first day of study (habituation phase), the rat was placed into an empty plastic box and could roam freely for 5 min. Next day, the rat was put into the same box but with two identical objects and could explore them for 3 min (familiarization phase). After a 5-min break, the short-term memory was evaluated and the animal was subjected to the trial with one familiar and one novel object for 3 min. After 24 hours, one of the objects was replaced with a new one and a similar trial was performed to assess the long-term memory. Directing the nose toward the object at a distance no more than 1 cm, touching or sniffing it with the nose were considered exploratory behavior. Sitting on objects or turning around on them were not defined as an exploration of the object. The box and objects were cleaned with 70% isopropyl alcohol between each trial to maintain the same fragrance. Memory was evaluated by the discrimination index (DI) defined as the following formula: (novel object (s)/novel object (s) + familiar object (s)) x 100%. DI value higher than 50% indicates preference of the novel object, lower than 50% – preference of the familiar object and around 50% – no preference.

2.6. Elevated plus maze test (EPM)

The test was performed according to the method described in [18]. Anxiety-like behavior was evaluated in an EPM apparatus consisting of two open arms (50 cm × 10 cm × 40 cm), a central platform (5 cm × 5 cm) and two closed arms (50 cm × 10 cm × 40 cm). The maze was located about 50 cm above the floor. The rat was placed in the central platform and allowed to move freely for 5 min, which was recorded using a camera mounted above the maze. The evaluated data included the time spent in the open arms, defined as a percentage of the total time spent in both the open and closed arms, the number of entries into the open arms, defined as a percentage of the total number of entries into both open and closed arms, and distance traveled. All four paws must be placed in the arm to record “the entry”. The anti-anxiety behavior reflects as an increase in the open-arm activity like longer time and/or more entries to open arms. The EPM apparatus was cleaned with 70% isopropyl alcohol between sessions to maintain the same fragrance.

2.7. Statistical analyses

The results were analyzed using Statistica 13.1 software. Parametric tests were used for parameters with normal distribution and homogeneity of variance (Student’s t-test). Non-parametric tests were used in the absence of any of the above conditions: the Mann–Whitney U-test was used to compare two groups (MWM, PA) and Friedman rank sums test in comparison within a group (MWM). A p-value of 0.05 or less indicated a statistically significant difference. Data are present as mean values ± SEM (parametric tests) or median (horizontal bar), first and third quartiles (vertical column) and minimum and maximum (vertical line) (non-parametric tests). Outlier values are represented with circles.

3. Results

3.1. Initial training before levetiracetam administration in the MWM

No memory impairment was observed in animals during training. The time needed to find the platform and traveled distance gradually shortened during the training in both groups. The time spent in the zone with the platform was longer during this period (figure not included).

3.2. The effect of levetiracetam administered at low dose on the spatial memory in rats in MWM

LEV administered at a single dose of 100 mg/kg p.o. did not affect the learning processes. No significant differences were found between groups in the trial time (Fig. 2A), distance (Fig. 2B) and time in the proper zone (Fig. 2C). The time needed to find the platform gradually shortened during the experiment in both the LEV and C groups, and significant differences were observed between test days 1 and 2 (respectively, p = 0.01963, p = 0.0091; Friedman test) and between test days 1 and 3 (respectively, p = 0.01141, p = 0.00091; Friedman test) (Fig. 2A). A significant decrease in time was also shown between test days 2 and 3 in the LEV group (p = 0.03481; Friedman test). The traveled distance also shortened and significant differences were observed between test days 1 and 2 (p = 0.01963; Friedman test) and 1 and 3 (p = 0.01141; Friedman test) in the LV group and between test days 1 and 2 (p = 0.00091; Friedman test), 1 and 3 (p = 0.00091; Friedman test) and 2 and 3 (p = 0.03481; Friedman test) in the control group (Fig. 2B). As shown in Fig. 2C, the percentage of the time spent by rats in the target zone significantly increased in both studied groups, compared to the initial values. Significant differences were observed on day 2 in the control group (p = 0.024412; Student’s t-test) and on day 3 in LEV and C groups (respectively p = 0.00923, p = 0.000452; Student’s t-test).

3.3. The effect of levetiracetam administered at high dose on the spatial memory in rats in MWM

The high dose of LEV (500 mg/kg p.o.) did not also alter memory parameters, compared to the control group. Fig. 3A shows a significant reduction in the time needed to find the platform on test days 2 and 3 in both LEV and C groups, compared to the initial values (respectively, p = 0.004061, p = 0.000145; p = 0.002769, p = 0.000014; Student’s t-test). Moreover, a significant decrease in time was also observed between test days 2 and 3 in the LEV group (p = 0.031846; Student’s t-test). The traveled distance decreased with each subsequent day of the study and statistically significant differences were observed between test days 1 and 2 in the C group (p = 0.000157; Friedman test) and between test days 1 and 3 in both LEV and C groups (respectively, p = 0.01141, p = 0.00091; Friedman test) (Fig. 3B). The time spent in the target zone also increased significantly in both groups on the third test day, and significant differences were observed compared to day 2 in the LV group (p = 0.047069; Student’s t-test) and day 1 in the LEV and C groups (respectively p = 0.004589, p = 0.000452; Student’s t-test). In the control group, a significant increase was also noted between test days 1 and 2 (p = 0.024412; Student’s t-test) (Fig. 3C).
3.4. The effect of prolonged administration of levetiracetam on the spatial memory in rats in MWM

Levetiracetam administered at dose of 300 mg/kg p.o. for two weeks did not affect the learning processes in rats. Only on the first day of the study, levetiracetam significantly shortened the distance traveled to find the platform compared to the control group ($p = 0.004939$; Student’s t-test). However, this effect did not occur on the following days of the study and then the results were comparable in both groups (Fig. 4B). A gradual reduction in the time needed to find the platform was observed and significant differences were noted between test days 1 and 3 in both the LEV and C groups (respectively, $p = 0.007977$, $p = 0.000235$; Student’s t-test) as well as between test days 1 and 2 in the C group ($p = 0.001642$; Student’s t-test) and 2 and 3 in the LV group ($p = 0.010309$; Student’s t-test) (Fig. 4A). A statistically significant shortening of the traveled distance was observed in the C group on the second and third test days, compared to the initial values (respectively $p = 0.002012$, $p = 0.000359$; Student’s t-test) (Fig. 4B). The percentage of time spent in the proper zone increased in both groups (Fig. 4C).

**Fig. 2.** Effect of acute administration of low dose of levetiracetam in MWM on the time needed to localize the platform (A), the distance traveled by rats in order to localize the platform – (B), the time spent in the zone with platform (C); LV – levetiracetam group, C – control group; *$p < 0.05$ (within a group); **$p < 0.01$ (within a group), ***$p < 0.001$ (within a group). A, B – data are present as median (horizontal bar), first and third quartiles (vertical column) and minimum and maximum (vertical line), outlier values are represented with circles; C – data are present as mean values ± SEM.
the LEV and C groups, and significant differences were seen between test days 1 and 3 (respectively, $p = 0.0027$, $p = 0.01963$; Friedman test) (Fig. 4 C).

3.5. The effect of levetiracetam administered at acute doses on the emotional memory in rats in PA

As shown in Fig. 5 A, LEV administered at a single dose of 100 mg/kg significantly decreased the step-through latency to escape to the dark compartment ($p = 0.030565$; the Mann–Whitney U-test). The same effect was observed after the high dose (500 mg/kg) of the drug ($p = 0.038040$; the Mann–Whitney U-test) (Fig. 5 B).

3.6. The effect of levetiracetam administered at prolonged dose on the emotional memory in rats in PA

LEV administered at 300 mg/kg p.o. for two weeks did not disturb the step-through latency, and the value of studied parameter was comparable in both groups (Fig. 5 C).

3.7. The effect of levetiracetam administered at prolonged dose on memory in NOR

LEV administered for three weeks did not alter the discrimination index in the short-term memory recognition test (Fig. 6 A). However, the rats spent significantly less time exploring the novel object in long-term memory recognition test, as compared to the C group ($p = 0.017673$; the Mann–Whitney U-test) (Fig. 6 B).
3.8. The effect of levetiracetam administered at prolonged dose on anxiety-like behavior in EPM

LEV administered for three weeks had no significant effect on anxiety in rats. The percentage of the time in open arms (Fig. 7A) and the percentage of the open-arm entries (Fig. 7B) were similar in the two studied groups. However, the traveled distance was significantly shorter in the LEV group ($p = 0.048575$; Student’s t-test) (Fig. 7C).

4. Discussion

Memory disturbances are common among patients with epilepsy [12]. Both first-generation and some newer antiseizure medications may cause memory impairment, decreased vigilance and psychomotor slowing [19]. Levetiracetam is one of the newest anticonvulsant drugs, with a unique mechanism of action associated with binding to protein SV2A [1] and blocking voltage-activated Ca2+ channels [2–4]. The drug has also neuroprotective activity related to decrease in oxidative stress and lipid peroxidation [20,21] as well as anti-inflammatory and antiapoptotic activities [22]. Recent studies on the use of the drug in the treatment of diseases associated with neuronal damage or loss have identified various beneficial effects, including those improving ischemic stroke [22], intracranial hemorrhage [23] or diabetic neuropathy [24]. An interesting direction of research is also the attempt to use levetiracetam in the treatment of diseases associated with memory deficits like Alzheimer’s disease [7–8] or alcohol dependence [11]. Moreover, some antiseizure medications have been successfully used in the treatment of mood disturbances and a few studies suggest that levetiracetam is effective in patients with anxiety disorders [5–6]. Hence, the aim of this study was to assess the effect of levetiracetam on various types of memory and anxiety in rats.

One of the research methods was the Morris water maze test, used to assess spatial memory and learning ability in rodents. The results show that LEV administered at an acute high (500 mg/kg) or low dose (100 mg/kg) did not alter spatial memory in rats. In both studied groups, the time needed to find the platform and the traveled distance were shorter with each subsequent test day. However, LV administered repeatedly for 14 days also had no adverse effect on the learning process in the animals. However, a significant decrease in swimming distance was noted on the first day of the experiment. This observation was not related with the reduced study time which, therefore, may indicate not a favorable effect but a disorder of animal locomotor activity. This effect was no longer noticeable in the following days of the test.
The passive avoidance test is a second behavioral model used to assess emotional memory. It is a fear-motivated test based on the acquisition, storage and maintenance of the memory of an aversive stimulus. LEV administered at a low or high dose decreased the step-through latency to escape to the dark compartment. This adverse effect seems to be temporary because impairment of memory acquisition was not observed after repeated administration of the drug. However, it cannot be excluded that avoidance behavior may be enhanced by an increased anxiety. Although, the research involving mice showed that more anxious DBA/2J strain demonstrate disturbance of avoidance learning in comparison to C57BL/6J mice [17,29]. In a previous study, the effect of LEV on memory and learning processes was evaluated using a passive avoidance test in mice receiving acute dose of the drug (17 or 54 mg/kg i.p.). The results indicated that both doses of the drug have an ameliorating effect on acquisition and memory formation [26]. In contrast, LEV administered repeatedly for 45 days (310 mg/kg p.o.) disturbed this type of memory in rats [28].

The third behavioral model used to achieve the aim was the novel object recognition (NOR) test. The NOR is very useful for studying short-term and long-term memory, through manipulation of the retention interval. It has been observed that LEV did not alter short-term memory but the drug disturbed the long-term recognition memory in rats. As all behavioral tests, NOR has also its limitations. The level of exploration can be low not only due to memory disorders but also because of wrong arena or object selection. The disturbances may occur as a result of the lack relevant differences between objects or anxiety of novel object [30]. In our study, the rats were habituated to the arena resembling a housing cage which should reduce the stress. The selected objects were different in shape, color, and height. However, height difference was not large so that the animal does not avoid a too large object or climb onto a too low object. To avoid the preference of place, half of the studied animals have novel object on the left side of the arena and the other half on the right side. The location of the new object for the selected rat was always the same on each study day.

In a recent study, Rehman et al. (2022) assessed the effect of LEV on memory in PTZ-kindled rats also using the NOR test. The drug was given i.p. at a dose of 50 mg/kg for 21 days. Contrary to our results, levetiracetam improved recognition memory which was associated with a greater exploration of the new object [31]. The drug was also investigated in a mouse model of chronic cerebral hypoperfusion. LV was given after bilateral common carotid artery stenosis (BCAS) at a dose of 150 mg/kg i.p. [28]. In another study, the effect of LV on anxiety was compared to the activity of its analog – brivaracetam. The anxiolytic activity of levetiracetam is also investigated nowadays. Our present findings indicate that the drug did not increase anxiety level in rats, but appeared to decrease locomotor activity.

In a previous study, LEV did not also affect spatial memory retrieval in naive mice. The drug was given acutely i.p. at a dose of 17 and 54 mg/kg [28]. The effect of levetiracetam on cognitive functions was also evaluated following status epilepticus (SE). The drug administered for 14 days at a dose of 50 mg/kg i.p. did not improve post-SE disturbance of learning processes [27]. In another study, cognitive impairment was observed after a 45-day administration of LV at a dose of 310 mg/kg p.o. This negative effect was associated with augmentation of oxidative stress. The authors highlight requirement for stringent pharmacovigilance, especially during long-term therapy [28].
evaluated using other behavioral models. Lamberty et al. (2003) evaluated the effect of LEV in the Vogel conflict test. The rats received the drug i.p. at the acute dose of 17 mg/kg and 54 mg/kg and a higher dose of the drug showed an anxiolytic effect similar to clordiazepoxide [35].

This study found repeated administration of LEV to have a disruptive effect on locomotor activity. However, the acute dose of the drug had no effect on locomotion [34,36]. Furthermore, other authors also observed that LEV administered repeatedly for 45 days did not alter locomotor activity in rats [28]. Moreover, pretreatment with LEV reduced also ethanol-induced locomotor stimulation and attenuated the development of locomotor sensitization to repeated exposure to alcohol. However, the opposite effect was observed on cocaine-related behaviors [36].

The observed lack of disturbances in short-term recognition, spatial and emotional memory in rats receiving repeated doses of levetiracetam indicates the absence of major negative impact on cognition. However, the associated disturbances in long-term recognition memory, locomotor activity, and emotional memory after an acute dose of the drug appear to be important aspects limiting its possible use. It should be emphasized that emotional memory disturbance was only temporary and did not occur after repeated administration. Due to the use of the naive rats in the experiment, the interpretation of the clinical aspect of the results is limited. For this reason, further studies are needed to expand knowledge about the safety of levetiracetam, especially in a model of AD or epilepsy-associated comorbidities.

Funding

This study was supported by a research Grant No: 502-34-095 from the Medical University, Łódź, Poland. The funding source had no other role other than financial support.

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.

References

[1] Lynch BA, Lambeng N, Nocka K, Kessel-Hamme P, Bajajilieh SM, Matagne A, et al. The synaptic vesicle protein SV2A is the binding site for the antiepileptic drug levetiracetam. Proc Natl Acad Sci USA 2004;101(26):9861–6. https://doi.org/10.1073/pnas.0308208101.

[2] Lee CY, Chen CC, Liou HH. Levetiracetam inhibits glutamate transmission through presynaptic P/Q-type calcium channels on the granule cells of the dentate gyrus. Br J Pharmacol 2009;158(7):1753–62. https://doi.org/10.1111/j.1476-5381.2009.04637.x.

[3] Lukyanetz EA, Shkryl VM, Kostyuk PG. Selective blocked of N-type calcium channels by levetiracetam. Epilepsia 2002;43:9–18. https://doi.org/10.1046/j.1528-1157.2002.24501.x.

[4] Van HD, Ishihara K, Seki T, Hanaya R, Kurisu K, Arita K, et al. Inhibitory effects of levetiracetam on the high-voltage-activated T-type Ca2+ channels in hippocampal CA3 neurons of spontaneously epileptic rat (SER). Brain Res Bull 2013;90(1):142–8. https://doi.org/10.1016/j.brainresbull.2012.10.006.

[5] Hagemann A, May TW, Nieder E, Witte-Bölt K, Pohlmann-Eden B, Elger CE. Zonisamide, topiramate, and levetiracetam: efficacy and neuropsychological effects in alcohol use disorders. J Clin Psychopharmacol 2015;35(1):34–42. doi:10.1097/JCP.0000000000000467.

[6] Rzezak P, Lima EM, Gargaro AC, Cembra E, de Vincentis S, Velasco TR, et al. Everyday memory impairment in patients with temporal lobe epilepsy caused by hippocampal sclerosis. Epilepsy Behav 2017;79:31–6. https://doi.org/10.1016/j.yebeh.2017.05.019.

[7] Bootmatic HPR, Ricker L, Diepman L, Gehring J, Hulsman J, Lambechts D, et al. Long-term effects of levetiracetam and topiramate in clinical practice: A head-to-head comparison. Seizure 2008;17(1):19–26. https://doi.org/10.1016/j.seizure.2007.05.019.

[8] Benedetti MS, Couppe R, Whomsley R, Nicolas JM, Collart P, Baltes E. Comparative pharmacokinetics and metabolism of levetiracetam, a new anti-epileptic agent, in mouse, rat, rabbit and dog. Xenobiotica 2004;34(3):281–300. https://doi.org/10.1080/0049825042000196749.

[9] Vossel K, Ranasinghe KG, Beagle AJ, La A, Ah Pook K, Castro M, et al. Effect of Levetiracetam on Cognition in Patients With Alzheimer Disease With and Without Epileptiform Activity: A Randomized Clinical Trial. JAMA Neurol 2012;69(11):1345.

[10] Zorumski CF, Mennerick S, Izumi Y. Acute and chronic effects of ethanol on learning-related synaptic plasticity. Alcohol 2014;48(1):1–17.

[11] Sanchez A, Cipriano D, Nardi-Seppa O, Richardson MA, Devine E, Streeter CC, Oscar-Berman M, Surprise C, Colantuoni L, Putnam M, Waters M, Richambaut C. Zonisamide, topiramate, and levetiracetam: efficacy and neuropsychological effects in alcohol use disorders. J Clin Psychopharmacol 2015;35(1):34–42. doi:10.1097/JCP.0000000000000467.

[12] Rodriguez-Hernandez J, Canales-Diego A, Delgado-Escueta V, Elghozi J, Garcia-Dominguez A, et al. Effect of levetiracetam on the expression of genes associated with mitochondrial function in hippocampal slices from rats. Epilepsy & Behavior 2013;23(1):79–87. https://doi.org/10.1016/j.yebeh.2012.10.029.

[13] Inaba T, Miyamoto N, Hira K, Ueno Y, Yamashiro K, Watanabe M, et al. Levetiracetam, an antiepileptic drug, reduces NMDA receptor activity in rat hippocampal CA3 neurons of spontaneously epileptic rat (SER). Brain Res 2007;1216:226–30. https://doi.org/10.1016/j.ybrsin.2007.05.019.

[14] Knapp CM, Ciraulo DA, Sarid-Segal O, Richardson MA, Devine E, Streeter CC, Oscar-Berman M, Surprise C, Colantuoni L, Putnam M, Waters M, Richambaut C. Zonisamide, topiramate, and levetiracetam: efficacy and neuropsychological effects in alcohol use disorders. J Clin Psychopharmacol 2015;35(1):34–42. doi:10.1097/JCP.0000000000000467.

[15] Sanchez PE, Zhu L, Verret L, Vossel KA, Orr AG, Cirrito JR, et al. Levetiracetam suppresses neuronal network dysfunction and reverses synaptic and cognitive deficits in an Alzheimer’s disease model. Proc Natl Acad Sci USA 2012;109(42):E2895–903. https://doi.org/10.1073/pnas.1210818110.

[16] Rehman Z, Farooq T, Javaid S, Ashraf W, Fawad Rasool M, Samad N, et al. Combination of levetiracetam with sodium selenite prevents pentyleneetetrazole-induced kindling and behavioral comorbidities in rats. Saudi Pharmaceutical J 2022;30(5):494–507.

[17] Inaba T, Miyamoto N, Hira K, Ueno Y, Yamashiro K, Watanabe M, et al. Protective Role of Levetiracetam Against Cognitive Impairment And Brain White Matter Damage in Mouse prolonged Cerebral Hypoperfusion.
[33] Pádua Carobrez A, Kincheski GC, Bertoglio LJ, et al. Elevated plus maze. In: Stolerman IP, editor. Encyclopedia of Psychopharmacology. Springer Science + Business Media; 2010. https://doi.org/10.1007/978-3-540-68706-1_150.

[34] Sanon NT, Gagné J, Wolf DC, Aboulamer S, Bosoi CM, Simard A, et al. Favorable adverse effect profile of brivaracetam vs levetiracetam in a preclinical model. Epilepsy Behav 2018;79:117–25. https://doi.org/10.1016/j.yebeh.2017.11.019.

[35] Lamberty Y, Falter U, Gower AJ. Antiepileptic drug levetiracetam in the Vogel conflict test in the rat. Eur J Pharmacol 2003;469(1–3):97–102. https://doi.org/10.1016/S0014-2999(03)01724-2.

[36] Robinson JE, Chen M, Stamatakis AM, Krouse MC, Howard EC, Faccidomo S, et al. Levetiracetam has opposite effects on alcohol- and cocaine-related behaviors in C57BL/6j mice. Neuropsychopharmacology 2013;38(7):1322–33. https://doi.org/10.1038/npp.2013.35.