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ARTICLE

The effect of vortioxetine on penicillin-induced epileptiform activity in rats

O efeito da vortioxetina sobre a atividade epileptiforme induzida pela penicilina em ratos

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ABSTRACT

Vortioxetine is a multimodal antidepressant agent that modulates 5-HT receptors and inhibits the serotonin transporter. It is indicated especially in cases of major depressive disorder related to cognitive dysfunction. There are many studies investigating the effects of antidepressants on the seizure threshold and short-term epileptic activity. However, the effect of vortioxetine on epileptic seizures is not exactly known. Our aim was to investigate the effects of vortioxetine on penicillin-induced epileptiform activity. Twenty-seven Wistar rats were divided into three groups: sham-control group, positive control group (diazepam), and vortioxetine group. After a penicillin-induced epilepsy model was formed in each of the three groups of animals, 0.1 ml of saline was administered to the control group, 0.1 ml (10 mg/kg) vortioxetine was administered in the vortioxetine group, and 0.1 mL (5 mg/kg) of diazepam was administered in the positive control group, intraperitoneally. The epileptic activity records were obtained for 120 minutes after the onset of seizure. There was no significant difference in spike wave activity between the vortioxetine and diazepam groups, whereas this was significantly reduced in the vortioxetine group compared with the controls. The administration of vortioxetine at a dose of 10 mg/kg immediately after the seizure induction significantly decreased the spike frequencies of epileptiform activity compared with the control group. No significant difference was found between the vortioxetine and positive controls. This study showed that vortioxetine reduces the number of acutely-induced epileptic discharges. Vortioxetine may be an important alternative for epileptic patients with major depressive disorder-related cognitive dysfunction.

Keywords: Epilepsy; penicillins; vortioxetine, rats.

RESUMO

A vortioxetina é um agente antidepressivo multimodal que modula os receptores 5HT e inibe o transportador de serotonina. Está indicada, principalmente nos casos de transtorno depressivo maior (TDM), relacionado à disfunção cognitiva. Existem muitos estudos que investigam os efeitos dos antidepressivos no limiar convulsivo e na atividade epiléptica de curto prazo. No entanto, o efeito da vortioxetina nas crises epilépticas não é exatamente conhecido. Nosso objetivo é investigar os efeitos da vortioxetina sobre a atividade epileptiforme induzida pela penicilina. Vinte e sete ratos Wistar foram divididos em três grupos, grupo controle-sham, grupo controle positivo (Diazepam) e grupo vortioxetina. Depois, 0,1 mg (10 mg / kg) de vortioxetina foi administrado no grupo vortioxetina, e 0,1 ml (5 mg / kg) / kg) de diazepam foi administrado no grupo de controle positivo intraperitonealmente. Os registros de atividade epiléptica foram obtidos durante 120 minutos após o início da convulsão. Não houve diferença significativa na atividade de pico entre o grupo de voritoxetina e diazepam, embora tenha sido significativamente reduzida no grupo de vortioxetina em comparação com os controles. A administração de vortioxetina na dose de 10 mg / kg imediatamente após a indução das convulsões diminuiu significativamente as frequências de espícula da atividade epileptiforme em comparação com o grupo controle. Nenhuma diferença significativa foi encontrada entre a vortioxetina e controles positivos. Este estudo mostrou que a vortioxetina reduz o número de descargas epilépticas agudamente induzidas. A vortioxetina pode ser uma alternativa importante para pacientes epilépticos com disfunção cognitiva relacionada à TDM.

Palavras-chave: Epilepsia; penicilinas; vortioxetina, ratos.

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Epilepsy, characterized by recurrent spontaneous seizures, is one of the most common neurological disorders. Epilepsy is not only a disease, but also a symptomatic condition caused by genetic factors, traumatic brain injury, central nervous system infections, stroke, or structural brain lesions including brain tumors. In spite of detailed investigations, the underlying etiology cannot be found in approximately 65% of patients[1,2].

Nowadays, there are about 50 million people who have active epilepsy with frequent seizures that require therapy. Approximately 30% of these patients are resistant to all known antiepileptic medications[3]. In addition, the side effect profiles of existing drugs used in antiepileptic treatment are quite extensive. Therefore, efforts to find more effective antiepileptic drugs with low side effect profiles and elucidate the mechanisms of epilepsy are still in progress today[1].

Vortioxetine is a multimodal agent that modulates 5-hydroxytryptamine (5-HT) receptors and inhibits the serotonin transporter[4]. It is indicated especially in cases of major depressive disorder (MDD) related to cognitive dysfunction. Vortioxetine acts as a 5-HT1B partial agonist, 5-HT1A agonist and, 5-HT3, 5-HT7 and 5-HT1D receptor antagonist. It is also a 5-HT re-uptake inhibitor[5]. In addition to all these effects, it indirectly modulates GABA and glutamate receptors. In some studies, it has been shown that vortioxetine reduces GABA transmission and increases glutamate transmission, but these effects were found to be site-specific. Indeed, while vortioxetine reduces GABAergic activity in the prefrontal cortex, which may explain the cognitive improvement in MDD, it increases GABAergic activity in the striatum[6]. Previous studies have shown that selective serotonin reuptake inhibitors (SSRIs) have anticonvulsant effects and increase the seizure threshold. Serotonergic insufficiency is thought to be associated with epileptogenesis in the light of these studies. It has been observed that SSRIs have anticonvulsant activity at low doses (therapeutic) and convulsant effects at higher doses. No clear mechanism has been established regarding these paradoxical effects on seizure[7,8,9].

The effect of vortioxetine on seizures may be different from SSRIs due to its multimodular effects. Epileptic seizures were observed in 1% of MDD patients without a known epileptic history in the efficacy studies of vortioxetine. Therefore, it is advised that vortioxetine should be used cautiously in patients with epilepsy[10,11]. However, the effect of vortioxetine on epileptic seizures is not precisely known. Unlike other antidepressants, vortioxetine is effective in patients with MDD accompanied by cognitive impairment[10]. Therefore, it may be a very important alternative in epileptic patients with depression. As a result, it is important to investigate the effects vortioxetine in epilepsy.

The purpose of the present study was to investigate, via electrocorticogram, the effects of intraperitoneally-administered vortioxetine on penicillin-induced epileptiform activity in anesthetized rats.

METHODS

Animals

Male Wistar rats (200–250 g, aged 8-10 weeks) were obtained from the Abant Izzet Baysal University, Experimental Animals Research Center, Bolu, Turkey, and four or five animals were housed together under standard laboratory conditions. They were kept at a constant room temperature (22 ± 2°C) under a 12/12-hour light/dark cycle. Rats were given *ad libitum* access to food and water. Experiments were performed between 8:00 a.m.–12:00 p.m. in the daylight period to minimize circadian variation. All animal experiments were carried out in accordance with the ethical guidelines of the Ethics Committee of the Abant Izzet Baysal University, and the NIH Guiding Principles in the Care and Use of Animals.

Surgical procedure

The animals were starved for 24 hours and were weighed before the experiment. A dose of 90/10 mg/kg xylazine/ketamine was administered intramuscularly to the animals as an anesthetic. After shaving from the top of the head to the back of ears, the head of the animal was fixed to the operation table. The scalp was opened about 3 cm in length in the rostrocaudal direction using a lancet. Electrocautery was used to prevent bleeding from the soft tissues under the scalp. The soft tissue on the left cortex was removed. The skull was thinned by a spinning motor making circular motions and the skull bone was removed. After removal of the cortex, two Ag/AgCl top electrodes were used for electrophysiological recording. The positive electrode was placed 1 mm anterior to the bregma line, and 2 mm lateral to the sagittal suture, and the negative electrode was placed 5 mm posterior to the bregma line and 2 mm lateral to the sagittal suture. For grounding, an Ag/AgCl clamp electrode was fixed to the right auricle by applying recording gel.

Drugs and seizure paradigms

A total of 27 Wistar rats were randomly divided into three groups: sham control group (n = 9), positive control group (diazepam, n = 9), and vortioxetine group (n = 9). All drugs were dissolved in 0.9% NaCl and administered intraperitoneally. Epileptic activity was stimulated by injecting 500 IU/2 µl intracortical penicillin into the somatomotor cortex with a Hamilton microinjection (701N, Hamilton Co., Reno, NV, USA). The injection coordinates were 2 mm lateral, 1 mm anterior, and 1.2 mm depth of the bregma line.

Experiments and electrophysiological assessment

After the penicillin-induced epilepsy model was formed in each of the three groups of animals, 0.1 ml of saline was administered intraperitoneally to the control group; and 0.1 ml (10 mg/kg) vortioxetine (Lundbeck A/S, Copenhagen, Denmark) was administered intraperitoneally following the

onset of epileptic seizures in the vortioxetine group. As a positive control, the diazepam group (Gedeon Richter, Hungary) received 0.1 mL (5 mg/kg) of diazepam intraperitoneally following the onset of epileptic seizures. The epileptic activity recorded by the electrodes was immediately transferred to the PowerLab 4/SP (ADInstruments, Australia) data acquisition unit by enhancing in the BioAmp (ADInstruments, Australia) interface. Analog signals obtained from the cortex with PowerLab were transformed into the digital form and then transferred to a computer for analysis. The records obtained by the PowerLab system were divided into five-minute intervals by macro program and the number of spike waves and the amplitude of waves, as well as the starting times of seizure, were evaluated. Records were obtained for 120 minutes after the onset of seizure.

Statistical analysis

Spike-wave frequency obtained from the records of each animal was calculated automatically by the software. The differences of spike-wave frequency measurements between the groups were examined using the Kruskal-Wallis test. Dunn's multiple comparison test was used for post hoc analysis. The SPSS v.22 program was used in the analyses. A p-value of less than 0.05 was considered statistically significant. A minimum sample size of nine was determined by performing a power analysis with an alpha value of 5% and a power of 80%.

RESULTS

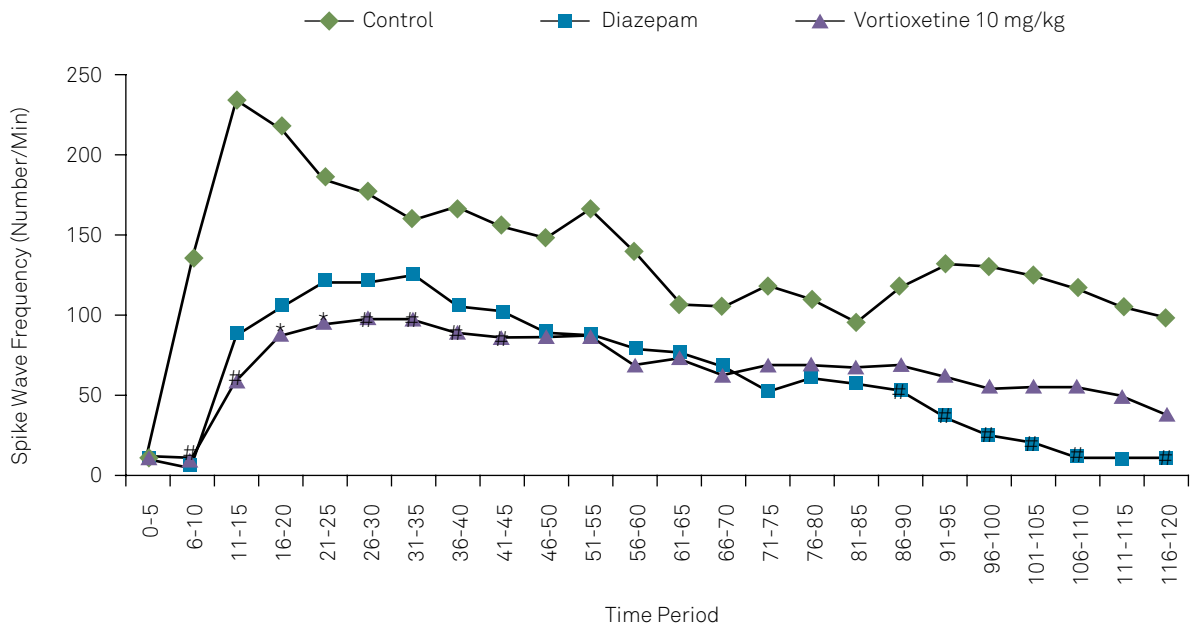
The median values of spike-wave frequency measured in the first five minutes of epileptic activity were found to be similar in each group (p = 0.407, Table). The median values of spike-wave frequency measured between the 6th and 120th minutes after the onset of epileptic activity were significantly different between groups, with some exceptions at certain time points (Table, Figure).

The differences between these groups were examined by multiple comparison tests. According to these results,

Table. The median values of spike-wave frequency (per minute) measured in the first five minutes of epileptic activity in each group.

Time (min)	n	Control		Diazepam		Vortioxetine		p-value
		Mean ± SEM	Median	Mean ± SEM	Median	Mean ± SEM	Median	
0–5	7	15.86 ± 2.352	12.00	14.00 ± 1.350	10.00	13.00 ± 2.803	11.50	0.407
06–10	7	134.57 ± 25.609	135.00	34.43 ± 30.424	6.00#	13.64 ± 5.093	11.50#	0.015
11–15	7	224.71 ± 20.977	234.00	73.29 ± 25.600	87.00#	61.64 ± 12.781	59.50#	0.009
16–20	7	220.43 ± 17.719	216.00	97.86 ± 17.376	105.00	87.50 ± 13.142	87.50*	0.013
21–25	7	234.71 ± 36.125	185.00	116.00 ± 14.305	120.00	197.50 ± 9.482	94.50*	0.020
26–30	7	212.71 ± 31.738	176.00	123.29 ± 23.011	120.00	95.50 ± 6.150	98.50#	0.038
31–35	7	185.00 ± 23.539	160.00	126.71 ± 27.705	125.00	95.64 ± 6.154	96.50#	0.049
36–40	7	176.14 ± 21.456	167.00	117.14 ± 27.670	106.00	96.36 ± 8.113	89.50#	0.049
41–45	7	167.00 ± 21.925	156.00	110.57 ± 27.514	101.00	93.29 ± 6.259	85.00#	0.049
46–50	7	169.71 ± 24.600	148.00	106.57 ± 24.903	89.00	95.50 ± 8.773	86.50	0.073
51–55	7	161.43 ± 22.977	166.00	100.43 ± 25.169	87.00	87.43 ± 9.868	87.00	0.114
56–60	7	146.00 ± 19.873	140.00	87.86 ± 20.973	80.00	8.36 ± 8.997	68.50	0.083
61–65	7	143.57 ± 23.536	107.00	80.86 ± 22.167	76.00	73.79 ± 6.966	72.50	0.062
66–70	7	137.00 ± 21.182	105.00	70.86 ± 21.459	68.00	87.43 ± 9.678	63.00	0.093
71–75	7	137.29 ± 21.366	118.00	61.00 ± 23.793	53.00	75.79 ± 11.116	68.50	0.057
76–80	7	126.00 ± 20.757	110.00	57.29 ± 23.149	61.00	72.79 ± 13.248	69.50	0.087
81–85	7	113.00 ± 18.364	95.00	54.71 ± 21.063	57.00	69.14 ± 11.805	67.00	0.110
86–90	7	130.86 ± 19.178	118.00	48.57 ± 19.587	53.00#	65.43 ± 12.436	68.00	0.034
91–95	7	128.57 ± 17.506	132.00	38.43 ± 17.015	37.00#	60.21 ± 12.134	61.50	0.016
96–100	7	132.14 ± 20.851	130.00	34.29 ± 16.037	25.00#	56.64 ± 11.681	54.50	0.009
101–105	7	126.00 ± 21.739	125.00	30.57 ± 15.035	20.00#	52.71 ± 11.328	55.00	0.009
106–110	7	116.57 ± 23.696	117.00	27.00 ± 14.358	12.00#	52.57 ± 11.968	55.00	0.021
111–115	7	102.86 ± 29.717	105.00	22.43 ± 12.051	10.00	49.36 ± 11.272	49.50	0.060
116–120	7	96.00 ± 28.377	98.00	23.14 ± 12.567	11.00 #	43.93 ± 12.853	37.50	0.048

* Indicates statistical difference compared to the control group [p ≤ 0.01]; # indicates statistical difference compared to the control group [p ≤ 0.05]).



* Indicates statistical difference compared to the control group [p ☙ 0.01]; # indicates statistical difference compared to the control group [p ☙ 0.05])

Figure. The median values of spike-wave frequency measured between the 6th and 120th minutes after the onset of epileptic activity were significantly different between groups with some exceptions at certain time points.

median values of spike-wave frequency measured in 6 to 10, 11 to 15, 16 to 20, 21 to 25, 26 to 30, 31 to 35, 36 to 40 and 41 to 45 minutes in the 10 mg/kg vortioxetine group were significantly lower than the values measured in the control group. (p = 0.05; p = 0.012; p = 0.008; p = 0.09; p = 0.020; p = 0.023; p = 0.028; p = 0.036, respectively). No statistically significant difference was found between the control group and the 10 mg/kg vortioxetine group between the 46th to 120th minutes in terms of spike-wave frequency (p > 0.05, Table). Similarly, the median values of the spike-wave frequency measured at 6 to 10, 11 to 15, 86 to 90, 91 to 95, 96 to 100, 101 to 05, 106 to 110 and 116 to 120 minutes in the diazepam group were significantly higher than the values measured in the control group (p = 0.021, p = 0.029, p = 0.049, p = 0.027, p = 0.028, p = 0.021, p = 0.036, p = 0.013, respectively). There was no significant difference between the groups for the rest of the experiment (Table). The diazepam and vortioxetine groups were similar throughout the experimental period.

DISCUSSION

To the best of our knowledge, this is the first study investigating the acute effects of vortioxetine on penicillin-induced epilepsy in the literature. There was no significant difference in spike-wave activity between the vortioxetine and diazepam groups, whereas spike-wave activity was significantly reduced in the vortioxetine group compared with the controls. The administration of vortioxetine at a dose of 10 mg/kg immediately after the seizure induction significantly decreased the spike frequencies of epileptiform activity compared with the control group. No significant difference was found between the vortioxetine and positive controls (diazepam 5 mg/kg).

The penicillin model is one of the most common models in experimental epilepsy researches[12]. Penicillin prevents the inhibitory effect of GABA by blocking the GABAA receptor[13]. This creates spike-wave activity in the electroencephalography, which then transforms into ictal discharges[14]. This effect of penicillin is observed in low doses and disappears in repeated doses[15]. There are many studies conducted with penicillin-induced epileptic seizure models in rats[16]. Rats were used in the present study because it was known that the rate of penicillin-induced epilepsy onset is higher in rats compared with other laboratory animals[12].

Diazepam is a short-acting benzodiazepine, which can be used acutely for penicillin-induced epilepsy model[17]. Therefore, diazepam was used as a positive control, as the acute effect of vortioxetine was being investigated in our study.

There are many studies investigating the effects of antidepressants on seizure threshold and short-term epileptic activity[8,9,18]. In most of the studies conducted with SSRIs, it has been shown that SSRIs increase the seizure threshold at low doses and reduce epileptic activity, but have the opposite effect at higher doses[19]. In a study conducted by Hernandez et al., it was observed that the five-day fluoxetine injection significantly reduced spontaneous recurrent seizures in the pilocarpine-induced status epilepticus model[20]. Specchio et al.[21] have shown that chronic citalopram treatment reduces seizure frequency. The effect of vortioxetine on seizures may be different from SSRIs due to its multimodular effects[5].

The 5-HT receptors are closely correlated with epilepsy; 5-HT1A, 5-HT2C, 5-HT3, 5-HT4 and 5-HT7 all play an important role in the development of epilepsy. Moreover, it is known that antiepileptic drugs increase the activity of extracellular 5-HT receptors[22,23,24,25]. It is considered that 5-HT receptors influence neuroexcitability by affecting the monoamine neurotransmitters GABA and glutamate, either directly or indirectly[26]. Of the 5-HT receptors, only the 5-HT3 receptors are ligand-gated ion channels that directly or indirectly change the ionic conduction and concentration, leading to neuronal depolarization. Studies have shown that 5-HT receptors are associated with pentylentetrazole-induced epilepsies[27]. Recent studies indicate that the most important pathways in epilepsy pathogenesis occurred in the entorhinal cortex, hippocampal c1 area, amygdala, substantia nigra, and brain stem, where 5-HT3 receptors are also distributed[25]. It is known that vortioxetine has an antagonistic effect on 5-HT3 receptor[5].

In the light of the information above, it can be stated that the effects of vortioxetine in reducing the epileptic discharge originated from its antagonistic effect on 5-HT3. Indeed, in our study, the number of epileptic spike waves in the vortioxetine group was significantly lower than that of the control group. Likewise, the numbers of spike waves were similar between vortioxetine and a positive control diazepam group. To our knowledge, there is no study investigating the effects of vortioxetine on seizures in the literature. However, in an efficacy study conducted by Mahableshwarkar et al.[10] on 611 patients, epileptic seizures were observed only in one patient at a therapeutic dose (5 mg/day). In animal studies conducted with vortioxetine, it has been shown that vortioxetine decreases GABA transmission and increases glutamate transmission, but this effect is site-specific. In other words, the opposite effect can be seen in some locations[28]. The most important limitation of our study is that different doses of vortioxetine were not studied. Different effects may be observed at different doses of vortioxetine when the dose-dependent effect of SSRIs on the seizure is considered.

Another limitation of our study was that the chronic effect of vortioxetine on epileptic seizure was not investigated. However, in previous studies, the effects of antidepressant drugs on seizure threshold and frequency have been investigated. Further studies are required to compare the efficacy of different doses of vortioxetine with other antidepressant drugs on seizure. Moreover, future studies will also require long-term follow up of patients to get more conclusive results.

In conclusion, this study showed that vortioxetine reduced the number of acutely-induced epileptic discharges. Vortioxetine, which is effective in patients with MDD-related cognitive dysfunction, may be an important alternative for epileptic patients with depression. However, long-term studies with different doses of vortioxetine are needed to provide more information on the use of this drug in epileptic patients. If it is demonstrated that vortioxetine is effective on some types of epilepsy, it may provide a safe and attractive treatment for people with epilepsy, particularly for those suffering from concurrent depression.

References

1. Beyazcicek E, Ankarali S, Beyazcicek O, Ankarali H, Demir S, Ozmerdivenli R. Effects of thymoquinone, the major constituent of Nigella sativa seeds, on penicillin-induced epileptiform activity in rats. Neurosciences. 2016 Apr;21(2):131-7. https://doi.or/10.17712/nsj.2016.2.20150781
2. Wong M. Epilepsy in a dish: an in vitro model of epileptogenesis. Epilepsy currents. 2011 Sep;11(5):153-4. https://doi.org/10.5698/1535-7511-11.5.153.
3. Ngugi AK, Kariuki S, Bottomley C, Kleinschmidt I, Sander J, Newton C. Incidence of epilepsy A systematic review and meta-analysis. Neurology. 2011 Sep;77(10):1005-12. https://doi.org/10.1212/WNL.0b013e31822cfc90
4. El Mansari M, Lecours M, Blier P. Effects of acute and sustained administration of vortioxetine on the serotonin system in the hippocampus: electrophysiological studies in the rat brain. Psychopharmacology (Berl). 2015 Jul;232(13):2343-52 https://doi.org/10.1007/s00213-015-3870-9.
5. Stahl SM. Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): modifying serotonin's downstream effects on glutamate and GABA (gamma amino butyric acid) release. CNS Spectr. 2015 Aug;20(4):331-6. https://doi.org/10.1017/S1092852915000334
6. Riga MS, Sánchez C, Celada P, Artigas F. Involvement of 5-HT3 receptors in the action of vortioxetine in rat brain: focus on glutamatergic and GABAergic neurotransmission. Neuropharmacology. 2016 Sep;108:73-81. https://doi.org/10.1016/j.neuropharm.2016.04.023
7. Bahremand A, Payandemehr B, Rahimian R, Ziai P, Pourmand N, Loloee S, et al. The role of 5-HT(3) receptors in the additive anticonvulsant effects of citalopram and morphine on pentylenetetrazole-induced clonic seizures in mice. Epilepsy Behav. 2011 Jun;21(2):122-7. https://doi.org/10.1016/j.yebeh.2011.03.010
8. Buchanan GF, Murray NM, Hajek MA, Richerson GB. Serotonin neurones have anti-convulsant effects and reduce seizure-induced mortality. J Physiol. 2014 Aug;592(19). https://doi.org/10.1113/jphysiol.2014.277574
9. Igelström KM, Heyward PM. The antidepressant drug fluoxetine inhibits persistent sodium currents and seizure-like events. Epilepsy Res. 2012 Aug;101(1-2):174-81. https://doi.org/10.1016/j.eplepsyres.2012.03.019
10. Mahableshwarkar AR, Jacobsen PL, Chen Y. A randomized, double-blind trial of 2.5 mg and 5 mg vortioxetine (Lu AA21004) versus placebo for 8 weeks in adults with major depressive disorder. Curr Med Res Opin. 2013 Mar;29(3):217-26. https://doi.org/10.1185/03007995.2012.761600
11. Wagner G, Schultes M-T, Titscher V, Teufer B, Klerings I, Gartlehner G. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: a systematic review and network meta-analysis. J Affect Disord. 2018 Mar 1;228:1-12. https://doi.org/10.1016/j.jad.2017.11.056

12. Edmonds HL, Stark LG, Hollinger MA. The effects of diphenylhydantoin, phenobarbital, and diazepam on the penicillin-induced epileptogenic focus in the rat. Exp Neurol. 1974 Nov;45(2):377-86. https://doi.org/10.1016/0014-4886(74)90126-5

13. Avanzini G, Franceschetti S. Cellular biology of epileptogenesis. Lancet Neurol. 2003 Jan;2(1):33-42. https://doi.org/10.1016/S1474-4422(03)00265-5 PMID:12849299

14. Wong R, Prince D. Dendritic mechanisms underlying penicillin-induced epileptiform activity. Science. 1979 Jun 15;204(4398):1228-31. https://doi.org/10.1126/science.451569

15. Ayala GF, Lin S, Vasconetto C. Penicillin as epileptogenic agent: its effect on an isolated neuron. Science. 1970 Feb;167(3922):1257-60. https://doi.org/10.1126/science.167.3922.1257

16. Arık AE, Bağırıcı F, Sefil F, Marangoz C. Effect of levetiracetam on penicillin induced epileptic activity in rats. Acta Neurobiol Exp (Wars). 2014;74(3):266-75.

17. Godlevsky L, Drozdova G, Kobolev E, Mustyatsa V, Polyasnyi V. Pentoxifylline potentiates antiepileptic activity of diazepam on the model of treatment-resistant focal epilepsy. Bulletin of experimental biology and medicine. 2013;154(3):326-8. https://doi.org/10.1007/s10517-013-1942-6

18. Cardamone L, Salzberg MR, Koe AS, Ozturk E, O'Brien TJ, Jones NC. Chronic antidepressant treatment accelerates kindling epileptogenesis in rats. Neurobiol Dis. 2014 Mar;63:194-200. https://doi.org/10.1016/j.nbd.2013.11.020

19. Mazarati A, Siddarth P, Baldwin RA, Shin D, Caplan R, Sankar R. Depression after status epilepticus: behavioural and biochemical deficits and effects of fluoxetine. Brain. 2008 Aug;131(Pt 8):2071-83. https://doi.org/10.1093/brain/awn117.

20. Hernandez EJ, Williams PA, Dudek FE. Effects of fluoxetine and TFMPP on spontaneous seizures in rats with pilocarpine-induced epilepsy. Epilepsia. 2002 Nov;43(11):1337-45. https://doi.org/10.1046/j.1528-1157.2002.48701.x

21. Specchio LM, Iudice A, Specchio N, La Neve A, Spinelli A, Galli R, et al. Citalopram as treatment of depression in patients with epilepsy. Clin Neuropharmacol. 2004 May-Jun;27(3):133-6. https://doi.org/10.1097/00002826-200405000-00009.

22. Panczyk K, Golda S, Waszkielewicz A, Zelaszczyk D, Gunia-Krzyzak A, Marona H. Serotonergic system and its role in epilepsy and neuropathic pain treatment: a review based on receptor ligands. Curr Pharm Des. 2015;21(13):1723-40. https://doi.org/10.2174/1381612821666141121114917.

23. Guiard BP, Giovanni GD. Central serotonin-2A (5-HT2A) receptor dysfunction in depression and epilepsy: the missing link? Front Pharmacol. 2015 Mar;6:46. https: doi: 10.3389/fphar.2015.00046

24. Youssof A-MA, Mourad HS, Reda AM, Farhan MS. Potential role of serotonin transporter gene (5-Htt) polymorphism in temporal lobe epilepsy susceptibility in egyptian patients. Egypt J Neurol Psychiatr Neurosurg. 2014;51(1):1-6. https:

25. Zhao H, Lin Y, Chen S, Li X, Huo H. 5-HT3 receptors: a potential therapeutic target for epilepsy. Curr Neuropharmacol. 2018;16(1):29-36. https://doi.org/10.2174/1570159X15666170508170412

26. Bagdy G, Kecskemeti V, Riba P, Jakus R. Serotonin and epilepsy. J Neurochem. 2007 Feb;100(4):857-73. https://doi.org/10.1111/j.1471-4159.2006.04277.x

27. Li B, Wang L, Sun Z, Zhou Y, Shao D, Zhao J, et al. The anticonvulsant effects of SR 57227 on pentylenetetrazole-induced seizure in mice. PLoS One. 2014;9(4):e93158. https://doi.org/10.1371/journal.pone.0093158

28. Pehrson AL, Jeyarajah T, Sanchez C. Regional distribution of serotonergic receptors: a systems neuroscience perspective on the downstream effects of the multimodal-acting antidepressant vortioxetine on excitatory and inhibitory neurotransmission. CNS Spectr. 2016 Apr;21(2):162-83. https://doi.org/10.1017/S1092852915000486