DOI: https://doi.org/10.54393/pjhs.v4i08.971

PAKISTAN JOURNAL OF HEALTH SCIENCES
https://thejas.com.pk/index.php/pjhs
Volume 4, Issue 8 (August 2023)

Review Article

Novel Approaches for Treatment of Epilepsy

Muhammad Ahsan Waqar[1*], Mehak Saleem[2], Tooba Mehboob[1], Naila Tabassam[1], Dawood Ilyas[3], Muhammad Sajid Nawaz[1], Mahnoor Foaad[1], Maria Riaz[1], Aimon Qureshi[1] and Muhammad Waqas[1]

[1]Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore, Pakistan
[2]Children's Hospital, Lahore, Pakistan
[3]School of Applied Sciences, University of Huddersfield, West Yorkshire, United Kingdom

ARTICLE INFO

Key Words:
Epilepsy, Corpus Callostomy, Neurostimulation, Surgery

How to Cite:
Waqar, M. A. ., Saleem, M. ., Mehboob, T. ., Tabassam, N. ., Ilyas, D., Nawaz, M. S. ., Foaad, M. ., Riaz, M. ., Qureshi, A. ., & Waqas, M. . (2023). Novel Approaches for Treatment of Epilepsy: Treatment of Epilepsy. Pakistan Journal of Health Sciences, 4(08). https://doi.org/10.54393/pjhs.v4i08.971

***Corresponding Author:**
Muhammad Ahsan Waqar
Faculty of Pharmaceutical Sciences, University of Central Punjab, Lahore, Pakistan
ahsanwaqar491@gmail.com

Received Date: 3rd August, 2023
Acceptance Date: 23rd August, 2023
Published Date: 31st August, 2023

ABSTRACT

Epilepsy is a serious neurological disorder on the juncture of psychiatry and neurology. It is characterized by recurrent and episodic seizures which are due to excessive discharge by the brain neurons. The therapeutic response failure of more than one or two antiepileptic drugs (AEDs) is the benchmark of refractory or intractable epilepsy. The aim of the study is to determine new approaches which lead towards the treatment of epilepsy. In order to treat focal mesial temporal lobe epilepsy or neocortical epilepsy in adults and any malformation of cortical development such as focal dysplasia surgical resection remains the gold standard treatment. Disconnection procedures such as corpus callostomy and multiple subpial transections are the best alternative treatment for that patient whose seizure origin is in eloquent cortex or having generalized epilepsy syndromes. Palliative neuromodulation procedures such as Vagus nerve stimulation (VNS), Responsive neurostimulation (RNS) and Deep brain stimulation (DBS) are best approach to treat intractable epileptic patients who are not suitable candidates of surgery. As the search of better management of epilepsy continues gene therapy and optogenetics gain a momentum in neuroscience.

INTRODUCTION

Epilepsy is one of the neurologic disorders that is characterized by recurrent episodic seizures. It can occur at all ages due to different causes [1]. In developed countries the incidence rate of epilepsy is 50 per 100,000 and prevalence rate is 5 to 10 per 1000. However, up to 30% people with epilepsy remain resistant to treatment despite treatment with monotherapy and polytherapy of antiepileptic drugs (AED). Time and countless effort have been invested by researchers to develop better treatment approaches such as antiepileptic devices, nano particles for targeting epileptic focus and gene therapy [2, 3]. There are five theories which explain the causes of thermoresistant epilepsy such as, transporter hypothesis, target hypothesis, gene variant hypothesis and the intrinsic severity hypothesis. The normal human brain is protected by P glycoprotein(P-gp), multi drug resistance gene 1(MDR1), which is found only in the vicinity of blood vessels on endothelial cell membrane that constitute BBB and multi drug resistance associate's protein 1 (MRP1), which is found only in the choroid plexus epithelium. Normally, P-glycoprotein(P-gp) export the drug out of cell in order to protect the cells against influx of xenobiotics. P-gp transport few AEDs, several AEDs have similar chemical structure to P-gp substrate [4, 5]. Hence it can be concluded that the inhibition of P-glycoprotein may contribute towards the treatment of patients suffering from antiepileptic drug resistant epilepsy [6]. Hence, researchers are of the view that the genetic variation of the

Copyright © 2023. PJHS, Published by Crosslinks International Publishers
This work is licensed under a Creative Commons Attribution 4.0 International License.

DOI: https://doi.org/10.54393/pjhs.v4i08.971

genes encoding enzymes that are responsible for metabolism of antiepileptic drugs, drug receptors and ion channels may be responsible for the resistance faced by some individuals in case of antiepileptic drug therapy [7, 8]. As shown in Figure 1, there are various novel treatment approaches for treating epilepsy. This study provides an extensive review of various novel treatment approaches (Figure 1) that have been used for the treatment of the epilepsy.

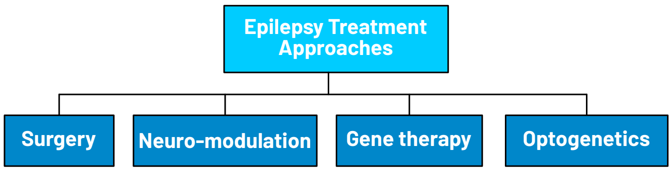

Figure 1: Various treatment approaches for epilepsy

SURGERY

Current AEDs which mainly targets ion channels and transmitter receptors are only effective in 60-70% of individuals idiopathic generalized epilepsy can be easily controlled by medication than the focal epilepsies and symptomatic generalized epilepsies [9, 10]. Epilepsy surgery can be divided into two categories, resective and disconnective procedures. The former includes lesionectomy, corticectomy, and lobectomy. The latter comprises MST (multiple subpial transections), corpus callosotomy, and hemispherotomy [11]. Surgical intervention need not be considered only as a last resort [12].

HEMISPHRECTOMY

The best candidates for hemisphrectomy are patients having progressive (Rasmussen's encephalitis and Sturge-Weber syndrome), acquired (e.g.; intracranial hemorrhage, hemiconvulsion-hemiplegia-epilepsy syndrome, and other sequelae of brain trauma and infection) developmental (e.g., cortical dysplasia, hemimegalencephaly) etiologies [13, 14]. Depending upon etiology and extension of anatomic abnormality there are three different surgical techniques.

Anatomic hemispherectomy

In anatomic hemisphrectomy lobes such as temporal, frontal, parietal and occipital lobes are removed with the preservation of the basal ganglia, insular cortex and thalamus.

Functional hemispherectomy

In functional hemispherectomy the procedures which are performed are (a) temporal lobectomy which extend to the trigone including hippocampus amygdala, (b) central excision in which lateral ventricle is exposed, (c) disconnection of corpus callosum from the ventricle to the course of anterior cerebral artery and pericallosal to the basal frontal region, and (d) posteriorly, corpus callosum is followed by subpial disconnection through temporal lobectomy to perform mesial parietooccipital disconnection.

Modified anatomic hemispherectomy

Modified anatomic hemispherectomy is similar to anatomic hemispherectomy but in modified anatomic hemispherectomy the disconnection of frontal or occipital lobes or both are preserved depending upon the etiology, anatomic abnormality and the location of epileptogenic zone. This progression began with the development of hemidecortication and functional hemisphrectomy in the 1970's and 1980's. further in 1990s several different approaches such as hemispherotomy was introduced [15-17].

Corpus Callostomy

Corpus Callostomy is a palliative surgical procedure which is performed in those patients who suffer from idiopathic generalized epilepsy (IGE) and are not the best suitable candidates of focal resection [18]. Seizures in IGE occur due to the absence of structural lesions or are inherited in nature [19]. Approximately in 40% to >70% of patient's seizure frequency and severity may reduce [20, 21]. In corpus callostomy complete section corpus callosum, anterior two third or three-fourth callostomy or anterior and posterior callostomy is performed. At present the most common procedure is two-third callostomy because of the less complications as compared to complete callostomy.

Multiple Subpial Transections (MST)

MST is one of the most novel approaches which are extensively used in those patients in which epileptogenic zone cannot be resected because it lies in eloquent cortex. In this method the horizontal connections which lies between the cortical neurons and are responsible for the propagation of the epileptic discharges is sectioned in this procedure [22]. MST can be performed alone or in combination with resective surgery such as a lesionectomy or large disconnections to treat epileptogenic foci present in eloquent cortex. MST not only treat unifocal epilepsy but also effective to treat Landau-Klefener Syndrome (LKS) in children and multifocal epilepsy in adults [23]. Hence, it was concluded that MST proved to be an alternative treatment for RSE [24].

NEUROMODULATION

Neuromodulation has become a major field of innovation in epilepsy therapy. Neuromodulation are palliative procedures which are minimal invasive and non-respective. In neuromodulation electrical pulses are directly administered to nervous tissue to stimulate a pathologic substrate in order to achieve a therapeutic effect (Figure 2). There are three neuromodulation techniques. Hence in case of such patient's neuromodulation is utilized [25].

Copyright © 2023. PJHS, Published by Crosslinks International Publishers
This work is licensed under a Creative Commons Attribution 4.0 International License.

DOI: https://doi.org/10.54393/pjhs.v4i08.971

VNS

Vagus nerve stimulation (VNS) as shown in Figure 2, is a neuromodulatory technique that stimulates the left vagus nerve [26]. Other than epilepsy, VNS is also use for mood improvements and for the treatment of drug resistant depression [27] hence VNS become a feasible treatment option in both neurology and psychiatry [28]. In worldwide more than 100,000 VNS devices were implanted in more than 75000 patients in August, 2014 [29]. In VNS battery-powered device which looks similar to cardiac pacemaker is implanted in the upper chest and electrodes with 2 connecting wires are placed subcutaneously to the left vagus nerve. The generator is connected by a wand and is attached with a laptop for monitoring. VNS is a broad-spectrum treatment and is very effective in refractory focal onset seizure patients. It can be used in those patients who already had surgical treatment.

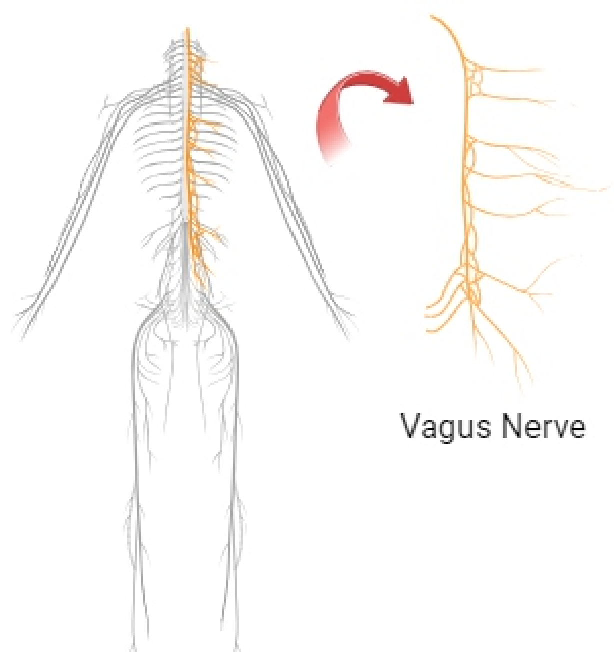

Figure 2: Vagus Nerve Stimulator

DBS

Deep brain stimulation (DBS) is one of the open loop systems. In DBS the target sites for stimulation are anterior nucleus of thalamus, centromedian thalamus, thalamus and seizure focus [30, 31]. Anterior nucleus deep brain stimulation (AN-DBS) was reported by copper and Upton for the first time. AN-DBS was introduced by these researchers for the treatment of complex partial seizures. The main idea behind this approach was the data collected over the year about the involvement of AN in the occurrence of generalized seizures [32]. Furthermore, it was concluded after research on animal-based models that high- frequency stimulation of AH may result in the increased seizure threshold or reduction in the frequency of seizures or both [33-35].

RNS

RNS is a closed loop stimulation which have an ability to stimulate the seizure focus automatically after the spontaneous detection of seizures. In this technique depth and subdural electrodes along with the neurostimulator is implanted in the cranium where seizure focus is located. According to a study performed by a group of researchers in 2011 concluded that there was a seizure reduction in intractable partial epileptic patients by receiving RNS [36]. RNS received FDA approval for the treatment of partial onset epilepsy in adults, in 2013 [25].

GENE THERAPY

In the past two decades advancement in technology and genetics led the researchers towards the discovery of almost 1000 genes solely associated with epilepsy [37]. Therefore, gene therapy (Figure 3) techniques can be used as an alternative to respective surgeries in case of patients suffering from intractable focal epilepsies. The main idea behind the gene therapy approaches is the transfer of therapeutic genes into the ictogenic areas of the brain. These therapeutic genes are involved in the expression of neuromodulatory molecules having special anticonvulsive and antiepileptic properties [38, 39].

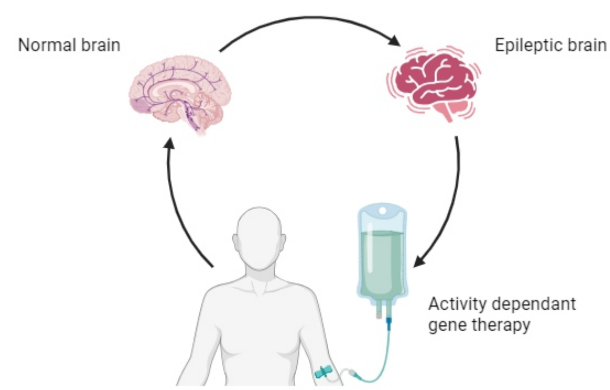

Figure 3: Gene Therapy

Neuropeptide System in Gene Therapy

Galanin in Gene Therapy

A12 neuropeptide system known as galanin system is most abundantly expressed in the temporal lobe of the brain. This system releases galanin which is a neuro peptide. Galanin acts by suppressing the excitatory glutamatergic neuronal transmissions which are involved in seizures [40]. Researchers developed viral vectors which act by exogenously releasing galanin in order to suppress the seizures. This approach was one of the first therapeutic approaches which are used to suppress seizures by the help of gene therapy [41].

NPY Gene Therapy

Copyright © 2023. PJHS, Published by Crosslinks International Publishers
This work is licensed under a Creative Commons Attribution 4.0 International License.

DOI: https://doi.org/10.54393/pjhs.v4i08.971

Neuropeptide Y (NPY) system is another neuropeptide system that is widely expressed in the brain. NPY naturally released in the brain by NPY system plays a vital role in controlling seizures [42]. Hence NPY is considered as a target candidate in case of antiepileptic gene therapy approach. Researchers are developing NPY gene therapy which will soon be entering the clinical trials for specifically treating temporal lobe epilepsy. This approach would prevent the surgical removal of ictogenic tissues [43].

OPTOGENETICS

Optogenetics is an evolution in the treatment of neurological disorders. It's a new advanced technique for the treatment of intractable epilepsy. Optogenetics is a combination of optical technology and gene targeting of neurons or proteins. If patients are not suitable candidates for surgery, then they are subjected to neuro stimulation such as VNS for the reduction of the seizure frequency. But if patients are suffering from post-surgical relapse, remission [44] or bilateral temporal lobe epilepsy or having seizure focus in eloquent cortex then they can get benefit from such an advanced and fascinating molecular-genetic tool which is known as Optogenetics. In this technique light sensitive proteins which are known as opsins are used [45, 46] which manipulate the brain activity. This fascinating approach can be used to treat epilepsy [47].

OTHER TREATMENTS OF EPILEPSY

Some other previous treatments used for treating epilepsy are mentioned in Table 1.

Table 1: Other Treatments of Epilepsy

Treatment Approaches	Interventions Used	Main Uses	References
Pharmaceutical approaches	Carbamazepine	Decrease nerve impulses that are responsible for causing seizures.	[48]
	Lamotrigine	Used as a first- line drug for generalized and focal seizures.	[49]
	Zonisamide	Used for generalized and focal seizures.	[48]
	Gabapentin	Used for generalized and focal seizures.	[48]
Therapeutic approaches	Cognitive Behavioural therapy	Restructuring of maladaptive thought patterns.	[50]
	Progressive muscle relaxation	Tense a group of muscles while breathing in and relaxes them while breathing out.	[51]
	Yoga	Release tension in key joints through combination of body postures.	[52]
Natural approaches	Herbal treatments	Found to be involved in potentiation of GABAergic activity in brain.	[53]
	Ketogenic diet	Neurotransmitter modulation in brain by ketone bodies.	[54]
	Vitamin D3	Increase Ca^{2+} uptake and decrease neuronal excitability.	[55]

CONCLUSIONS

There are many approaches to treat epilepsy. Among all approaches surgical treatment remain the gold standard to treat temporal lobe epilepsy, any malformation in cortical development or to treat any lesion. Alternative treatments for those patients who are not suitable candidates for resective surgery is neuromodulation. There are three types of neuro modulation and all of them are safe and effective in terms of reducing frequency of seizures. The best candidates for RNS and DBS are those patients whose seizure origin is in eloquent cortex. Optogenetics proved to be very effective in animal models to reduce the frequency of seizure. However, still some research such as optimization of light delivery, opsin introduction is required to be done before its application in humans.

Authors Contribution

Conceptualization: MAW, MS, MF

Writing-review and editing: MAW, MS, MF, TM, MSN, NT, DI, MR, AQ, MW

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The authors received no financial support for the research, authorship and/or publication of this article.

REFERENCES

[1] Duncan JS, Sander JW, Sisodiya SM, Walker MC. Adult Epilepsy. The Lancet. 2006 Feb; 367(9516): 1087-100. doi: 10.1016/S0140-6736(06)68477-8.

[2] Ramaratnam S, Marson AG, Baker GA. Lamotrigine add-on for drug-resistant partial epilepsy. The Cochrane Database of Systematic Reviews. 2001 Jan; 1(3): CD001909-. doi: 10.1002/14651858.Cd001909.

[3] Munir M, Zaman M, Waqar MA, Hameed H, Riaz T. A comprehensive review on transethosomes as a novel vesicular approach for drug delivery through transdermal route. Journal of Liposome Research. 2023 Jun: 1-6. doi: 10.1080/08982104.2023.2221354.

[4] Dalic L and Cook MJ. Managing drug-resistant epilepsy: challenges and solutions. Neuropsychiatric Disease and Treatment. 2016 Oct; 12: 2605-16. doi: 10.2147/NDT.S84852.

[5] Sisodiya SM, Lin WR, Harding BN, Squier MV, Thom M. Drug resistance in epilepsy: expression of drug resistance proteins in common causes of refractory

Copyright © 2023. PJHS, Published by Crosslinks International Publishers
This work is licensed under a Creative Commons Attribution 4.0 International License.

DOI: https://doi.org/10.54393/pjhs.v4i08.971

epilepsy. Brain. 2002 Jan; 125(1): 22-31. doi: 10.1093/brain/awf002.
[6] Löscher W, Klitgaard H, Twyman RE, Schmidt D. New avenues for anti-epileptic drug discovery and development. Nature Reviews Drug Discovery. 2013 Oct; 12(10): 757-76. doi: 10.1038/nrd4126.
[7] Tang F, Hartz AM, Bauer B. Drug-resistant epilepsy: multiple hypotheses, few answers. Frontiers in Neurology. 2017 Jul; 8: 301. doi: 10.3389/fneur.2017.00301.
[8] Waqar MA, Riaz T, Munir M, Ashfaq A, Zulfiqar H, Sandhu M, *et al*. COVID-19 and Various Comorbidities: A Review: COVID-19 and Various Comorbidities. Pakistan Journal of Health Sciences. 2023 Jan; 4(1): 02-7. doi: 10.54393/pjhs.v4i01.485.
[9] Brodie MJ and Kwan P. Staged approach to epilepsy management. Neurology. 2002 Apr; 58(8 suppl 5): S2-8. doi: 10.1212/WNL.58.8_suppl_5.S2.
[10] Brodie MJ. Medical therapy of epilepsy: when to initiate treatment and when to combine? Journal of Neurology. 2005 Feb; 252: 125-30. doi: 10.1007/s00415-005-0735-x.
[11] Shimizu H. Surgical treatment for intractable epilepsy. Rinsho Shinkeigaku= Clinical Neurology. 2001 Dec; 41(12): 1094-6.
[12] Engel Jr J. Surgery for seizures. New England Journal of Medicine. 1996 Mar; 334(10): 647-53. doi: 10.1056/NEJM199603073341008.
[13] Devlin AM, Cross JH, Harkness W, Chong WK, Harding B, Vargha-Khadem F, *et al*. Clinical outcomes of hemispherectomy for epilepsy in childhood and adolescence. Brain. 2003 Mar; 126(3): 556-66. doi: 10.1093/brain/awg052.
[14] González-Martínez JA, Gupta A, Kotagal P, Lachhwani D, Wyllie E, Lüders HO, *et al*. Hemispherectomy for catastrophic epilepsy in infants. Epilepsia. 2005 Sep; 46(9): 1518-25. doi: 10.1111/j.1528-1167.2005.53704.x.
[15] Shimizu H and Maehara T. Modification of peri-insular hemispherotomy and surgical results. Neurosurgery. 2000 Aug; 47(2): 367-73. doi: 10.1097/00006123-200008000-00018.
[16] Shimizu H and Maehara T. Neuronal disconnection for the surgical treatment of pediatric epilepsy. Epilepsia. 2000 Sep; 41: 28-30. doi: 10.1111/j.1528-1157.2000.tb02216.x.
[17] Schramm J, Behrens E, Entzian W. Hemispherical deafferentation: an alternative to functional hemispherectomy. Neurosurgery. 1995 Mar; 36(3): 509-16. doi: 10.1227/00006123-199503000-00010.
[18] Maehara T and Shimizu H. Surgical outcome of corpus callosotomy in patients with drop attacks. Epilepsia. 2001 Jan; 42(1): 67-71. doi: 10.1046/j.1528-1157.2001.081422.x.
[19] Jenssen S, Sperling MR, Tracy JI, Nei M, Joyce L, David G, *et al*. Corpus callosotomy in refractory idiopathic generalized epilepsy. Seizure. 2006 Dec; 15(8): 621-9. doi: 10.1016/j.seizure.2006.09.003.
[20] Nei M, O'Connor M, Liporace J, Sperling MR. Refractory generalized seizures: response to corpus callosotomy and vagal nerve stimulation. Epilepsia. 2006 Jan; 47(1): 115-22. doi: 10.1111/j.1528-1167.2006.00377.x.
[21] Asadi-Pooya AA and Sperling MR. Strategies for surgical treatment of epilepsies in developing countries. Epilepsia. 2008 Mar; 49(3): 381-5. doi: 10.1111/j.1528-1167.2007.01383.x.
[22] Ntsambi-Eba G, Vaz G, Docquier MA, van Rijckevorsel K, Raftopoulos C. Patients with refractory epilepsy treated using a modified multiple subpial transection technique. Neurosurgery. 2013 Jun; 72(6): 890-8. doi: 10.1227/NEU.0b013e31828ba750.
[23] Devinsky O, Romanelli P, Orbach D, Pacia S, Doyle W. Surgical treatment of multifocal epilepsy involving eloquent cortex. Epilepsia. 2003 May; 44(5): 718-23. doi: 10.1046/j.1528-1157.2003.57102.x.
[24] D'Giano CH, GARCıA MD, Pomata H, Rabinowicz AL. Treatment of refractory partial status epilepticus with multiple subpial transection: case report. Seizure. 2001 Jul; 10(5): 382-5. doi: 10.1053/seiz.2001.0521.
[25] Chang EF, Englot DJ, Vadera S. Minimally invasive surgical approaches for temporal lobe epilepsy. Epilepsy & Behavior. 2015 Jun; 47: 24-33. doi: 10.1016/j.yebeh.2015.04.033.
[26] Bailey P and Bremer F. A sensory cortical representation of the vagus nerve: with a note on the effects of low blood pressure on the cortical electrogram. Journal of Neurophysiology. 1938 Sep; 1(5): 405-12. doi: 10.1152/jn.1938.1.5.405.
[27] Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. Epilepsy & Behavior. 2000 Apr; 1(2): 93-9. doi: 10.1006/ebeh.2000.0046.
[28] Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, *et al*. VNS therapy in treatment-resistant depression: clinical evidence and putative neurobiological mechanisms. Neuropsychopharmacology. 2006 Jul; 31(7): 1345-55. doi: 10.1038/sj.npp.1301082.
[29] Chakravarthy K, Chaudhry H, Williams K, Christo PJ. Review of the uses of vagal nerve stimulation in chronic pain management. Current Pain and Headache Reports. 2015 Dec; 19: 1-9. doi:

Copyright © 2023. PJHS, Published by Crosslinks International Publishers
This work is licensed under a Creative Commons Attribution 4.0 International License.

DOI: https://doi.org/10.54393/pjhs.v4i08.971

10.1007/s11916-015-0528-6.
[30] Velasco F, Velasco AL, Velasco M, Jimenez F, Carrillo-Ruiz JD, Castro G. Deep brain stimulation for treatment of the epilepsies: the centromedian thalamic target. Operative Neuromodulation: Volume 2: Neural Networks Surgery. 2007:337-42. doi: 10.1007/978-3-211-33081-4_38.
[31] Lozano AM, Lipsman N, Bergman H, Brown P, Chabardes S, Chang JW, Matthews K, McIntyre CC, Schlaepfer TE, Schulder M, Temel Y. Deep brain stimulation: current challenges and future directions. Nature Reviews Neurology. 2019 Mar; 15(3): 148-60. doi: 10.1038/s41582-018-0128-2.
[32] Cooper IS, Upton AR, Amin I. Reversibility of chronic neurologic deficits. Some effects of electrical stimulation of the thalamus and internal capsule in man. Stereotactic and Functional Neurosurgery. 1980 May; 43(3-5): 244-58. doi: 10.1159/000102263.
[33] Mirski MA and Fisher RS. Electrical stimulation of the mammillary nuclei increases seizure threshold to pentylenetetrazol in rats. Epilepsia. 1994 Nov; 35(6): 1309-16. doi: 10.1111/j.1528-1157.1994.tb01803.x.
[34] Tyvaert L, Chassagnon S, Sadikot A, LeVan P, Dubeau F, Gotman J. Thalamic nuclei activity in idiopathic generalized epilepsy: an EEG-fMRI study. Neurology. 2009 Dec; 73(23): 2018-22. doi: 10.1212/WNL.0b013e3181c55d02.
[35] Moeller F, Siebner HR, Wolff S, Muhle H, Boor R, Granert O, *et al*. Changes in activity of striato–thalamo–cortical network precede generalized spike wave discharges. Neuroimage. 2008 Feb; 39(4): 1839-49. doi: 10.1016/j.neuroimage.2007.10.058.
[36] Dalkilic EB. Neurostimulation devices used in treatment of epilepsy. Current Treatment Options in Neurology. 2017 Feb; 19(2): 7. doi: 10.1007/s11940-017-0442-9.
[37] Demarest ST and Brooks-Kayal A. From molecules to medicines: the dawn of targeted therapies for genetic epilepsies. Nature reviews Neurology. 2018 Dec; 14(12): 735-45. doi: 10.1038/s41582-018-0099-3.
[38] McCown TJ. Adeno-associated virus (AAV) vectors in the CNS. Current gene therapy. 2005 Jun; 5(3): 333-8. doi: 10.2174/1566523054064995.
[39] Waqar MA, Qureshi A, Ahsan A, Sadaqat S, Zulfiqar H, Razaq A, *et al*. Epidemiology, Clinical Manifestations, Treatment Approaches and Future Perspectives of Rift Valley Fever: Epidemiology of Rift Valley Fever. Pakistan Journal of Health Sciences. 2023 Apr; 4(4): 02-8. doi: 10.54393/pjhs.v4i04.603.
[40] Mazarati AM and Wasterlain CG. Anticonvulsant effects of four neuropeptides in the rat hippocampus during self-sustaining status epilepticus. Neuroscience Letters. 2002 Oct; 331(2): 123-7. doi: 10.1016/S0304-3940(02)00847-9.
[41] Mazarati AM. Galanin and galanin receptors in epilepsy. Neuropeptides. 2004 Dec; 38(6): 331-43. doi: 10.1016/j.npep.2004.07.006.
[42] Erickson JC, Clegg KE, Palmiter RD. Sensitivity to leptin and susceptibility to seizures of mice lacking neuropeptide Y. Nature. 1996 May; 381(6581): 415-8. doi: 10.1038/381415a0.
[43] Sørensen AT and Kokaia M. Novel approaches to epilepsy treatment. Epilepsia. 2013 Jan; 54(1): 1-0. doi: 10.1111/epi.12000.
[43] Song C and Knöpfel T. Optogenetics enlightens neuroscience drug discovery. Nature Reviews Drug Discovery. 2016 Feb; 15(2): 97-109. doi: 10.1038/nrd.2015.15.
[45] Zhang F, Gradinaru V, Adamantidis AR, Durand R, Airan RD, De Lecea L, *et al*. Optogenetic interrogation of neural circuits: technology for probing mammalian brain structures. Nature Protocols. 2010 Mar; 5(3): 439-56. doi: 10.1038/nprot.2009.226.
[46] Yizhar O, Fenno LE, Davidson TJ, Mogri M, Deisseroth K. Optogenetics in neural systems. Neuron. 2011 Jul; 71(1): 9-34. doi: 10.1016/j.neuron.2011.06.004.
[47] Deisseroth K. Optogenetics. Nature Methods. 2011 Jan; 8(1): 26-9. doi: 10.1038/nmeth.f.324.
[48] Ventola CL. Epilepsy management: newer agents, unmet needs, and future treatment strategies. Pharmacy and Therapeutics. 2014 Nov; 39(11): 776.
[49] Schmidt D and Schachter SC. Drug treatment of epilepsy in adults. Bmj. 2014 Feb; 348. doi: 10.1136/bmj.g254.
[50] Ramaratnam S, Baker GA, Goldstein LH. Psychological treatments for epilepsy. Cochrane Database of Systematic Reviews. 2008 Jul; 3: 1-33. doi: 10.1002/14651858.CD002029.pub3.
[51] Haut SR, Gursky JM, Privitera M. Behavioral interventions in epilepsy. Current Opinion in Neurology. 2019 Apr; 32(2): 227-36. doi: 10.1097/WCO.0000000000000661.
[52] Panebianco M, Sridharan K, Ramaratnam S. Yoga for epilepsy. Cochrane Database of Systematic Reviews. 2017 Oct; 10: 1-37. doi: 10.1002/14651858.CD001524.pub3.
[53] Longo R, Peri C, Cricrì D, Coppi L, Caruso D, Mitro N, *et al*. Ketogenic diet: a new light shining on old but gold biochemistry. Nutrients. 2019 Oct; 11(10): 2497. doi: 10.3390/nu11102497.
[54] Liu W, Ge T, Pan Z, Leng Y, Lv J, Li B. The effects of herbal medicine on epilepsy. Oncotarget. 2017 Jul; 8(29): 48385. doi: 10.18632/oncotarget.16801.
[55] Holló A, Clemens Z, Kamondi A, Lakatos P, Szűcs A.

Copyright © 2023. PJHS, Published by Crosslinks International Publishers
This work is licensed under a Creative Commons Attribution 4.0 International License.

DOI: https://doi.org/10.54393/pjhs.v4i08.971

Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. Epilepsy & Behavior. 2012 May; 24(1): 131-3. doi: 10.1016/j.yebeh.2012.03.011.

Copyright © 2023. PJHS, Published by Crosslinks International Publishers
This work is licensed under a Creative Commons Attribution 4.0 International License.