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REVIEW ARTICLE

Drug-Resistant Epilepsy and Surgery

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Abstract: ***Background*:** Epilepsy is a chronic brain disease that is caused by various factors and characterized by recurrent, episodic and temporary central nervous system dysfunction which results due to excessive discharge of brain neurons. In the past decades, despite the continuous development of antiepileptic drugs, there are still many patients with epilepsy progressing to drug-resistant epilepsy. Currently, surgical treatment is one of important way to cure drug-resistant epilepsy.

***Methods*:** Data were collected from Web of Science, Medline, Pubmed, through searching of these keywords: "surgery" and "drug-resistant epilepsy".

***Results*:** An increasing number of studies have shown that surgery plays an important role in the treatment of drug-resistant epilepsy. Moreover, the comprehensive treatment mainly based on surgery can achieve the remission and even cure of drug-resistant epilepsy.

***Conclusion*:** In this review, we discuss the pathogenesis of drug-resistant epilepsy and the comprehensive treatment mainly based on surgery; this review may provide a reference for the clinical treatment of drug-resistant epilepsy.

Keywords: Drug-resistant, epilepsy, surgery, treatment, neuron, brain.

1. INTRODUCTION

Epilepsy is a chronic brain disease that is caused by various factors and characterized by recurrent, episodic and temporary central nervous system dysfunction which results from excessive discharge of brain neurons [1]. As a serious health problem worldwide, epilepsy accounts for 1% of the world's diseases [2]. In the past few decades, despite the continuous development of antiepileptic drugs, there are still more than 30% patients with epilepsy progressing to drug-resistant epilepsy [3], which leads to a significant increase in the morbidity and mortality of epilepsy. Drug-resistant epilepsy may be defined by International League Against Epilepsy (ILAE) as failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [4]. Currently, surgical treatment may be the only possible way to cure drug-resistant epilepsy. However, due to the complicated etiology and unclear pathogenesis of drug-resistant epilepsy, surgical treatment alone is always difficult to achieve a radical effect, and antiepileptic comprehensive treatment mainly based on surgery needs to be combined with other treatment methods. The present paper mainly reviews the pathogenesis of drug-resistant epilepsy and the comprehensive treatment mainly based on surgery, which provides a reference and guidance for the clinical treatment of drug-resistant epilepsy.

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2. PATHOGENESIS OF DRUG-RESISTANT EPILEPSY

The pathogenesis of epilepsy is complex and, at present, commonly acknowledged to be caused by the excitatory and inhibitory imbalance of the central nervous system. So far, the hypotheses regarding the pathogenesis of drug-resistant epilepsy mainly include transporter hypothesis, target hypothesis, *etc*.

2.1. Transporter Hypothesis

Most antiepileptic drugs play the antiepileptic role in the brain *via* the blood-brain barrier [5]. Moreover, the overexpression of multidrug transporters that have a role in the efflux from the capillary endothelial cells which form the blood-brain barrier may lead to increased intracellular drug efflux or isolated vesicles, resulting in decreased intracellular drug concentration or changed drug distribution; consequently, antiepileptic drugs in epileptogenic zone and surrounding tissues cannot achieve the effective drug concentration, which leads to drug resistance [6]. At present, multidrug

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transporters that are frequently studied include P-glycoprotein (P-gp), multidrug resistance protein (MRP), breast cancer resistance protein (BCRP) [7]. Some common drugs, such as carbamazepine, felbamate, gabapentin, lamotrigine, phenobarbital, phenytoin and topiramate, are all substrates of P-glycoprotein; meanwhile, phenytoin is substrates of multidrug resistance protein-2 (MRP2) [8, 9]. Kerstin Römermann *et al*. found that lamotrigine is a substrate of BCRP, which is evidenced in this hypothesis [10].

2.2. Target Hypothesis

Target hypothesis proposes that antiepileptic drugs cannot inhibit the excessive discharge of neurons through binding the predetermined target when the structure or function of the target of antiepileptic drugs changes, resulting in uncontrollable epilepsy attack, which is mainly reflected by abnormal ion channel function [11]. Currently, it has been confirmed that the voltage-gated sodium channel (VGSC) is mainly expressed in excitatory cells, and is the main target of the traditional first-line AEDs [12]. Research has proved that SCN1A gene (coding for the sodium channel, neuronal type I, alpha subunit) mutation is the main pathogenic gene of severe myoclonic epilepsy in infancy [13]. In addition, the model experiment of gene knockout mice for simulating human channel diseases has verified that SCN1A mutation causes reduced expression level of sodium channel subtype Nav1.1, leading to decreased excitatory of inhibitory neurons, functional decline in inhibitory loop and increased neuronal excitability, which are necessary for the onset of epileptic seizures [14]. Sodium channel gene mutations cause the loss of partial functional targets of the AEDs, decreased amplitude and duration of inhibitory sodium current, increased excitability of the whole neural network, and action potential spreading to the whole or partial brain, and thereby forming epileptic discharge. Also, Escayg A *et al*. compared 226 patients with drug-resistant epilepsy and 185 controls, revealing that the proportion of SCN1A mutations in the patients with drug-resistant epilepsy was significantly higher than that in the control group [15].

3. SURGICAL TREATMENT OF DRUG-RESISTANT EPILEPSY

Although there were multiples of new-type antiepileptic drugs that have been continued to be approved for application, there still exist more than 30 percent of patients with epilepsy developed into drug-resistant epilepsy [3]. Wiebe S *et al*. conducted an RCT research and proved that the one year cure rate of patients with temporal lobe epilepsy by surgical treatment was significantly higher than that by drugs treatment (58% vs. 8%), which proved that surgical operation might be workable for the control of the incidence of temporal lobe epilepsy [16]. In addition, Fiest KM *et al*. found that patients at 6 months after surgery in the surgical group achieved positive minimum clinically important change (MCID) on the Quality of Life in Epilepsy (QOLIE)-89, compared with those in the medical group (56.0% *vs*. 11.0%,$p < 0.001$), meanwhile 62.0% of the surgical group achieved positive MCID on the QOLIE-31 ($p < 0.001$) compared with 17.0% of the medical group [17]. With the continuous development of related science and technology, a variety of different surgical treatment methods emerged in response to the proper time and conditions, and now surgical treatment has become a very important therapeutic tool for drug-resistant epilepsy treatment. The goal of surgery is to reduce the seizures, to avoid the adverse reaction after surgery, and to a certain extent, to improve the quality of life. In general, we need to adjust the preoperative state of patients to meet the criteria of surgery. At present, surgical treatment methods for epilepsy are divided into resective surgery, palliative surgery, neurostimulation and other surgical interventions.

3.1. Resective Surgery

Temporal lobe epilepsy is the most common type of drug-resistant epilepsy, which is usually treated by surgical operation [18]. Resective surgeries are gradually recognized to be the major treatment choice for drug-resistant epilepsy based on a large numbers of clinical experiments, and the early mesial temporal lobe epilepsy is particularly recommended to be treated by surgical operation [19, 20].

3.1.1. Mesial Temporal Lobe Epilepsy Resection

Surgical treatment methods for mesial temporal lobe epilepsy include anterior temporal lobectomy and selective amygdalohippocampectomy. In a long-term research which involved 615 cases of epilepsy patients, there were approximately 52% (95%CI, 48 to 56) patients who had no recurrence of seizures even after five years of surgery, and about 47% (95%CI, 42 to 51) patients did not indicate any signs of epilepsy attacks ten years postoperatively [21]. The study of RCT, Jerome Engel Jr, MD PhD *et al*. indicated that antiepileptic integrated therapy mainly based on surgical treatment showed a significantly greater efficacy in epilepsy patients escaping from relapse after treatment for two years than those received continues drugs treatment (OR = ∞; 95% CI, 11.8 to ∞; $P < 0.001$). The Quality of Life (QOL) overall T-score of patients in the surgical group was significantly higher than that in the medical group (12.8 points vs. 2.8 points; treatment effect =9.9; 95% CI, 2.2 to 17.7; $P = 0.01$) [19].

Anterior temporal lobectomy is applicable for cases with epileptogenic zones on one side of the temporal lobe [22]. As almost all of epilepsy lesions of the mesial temporal lobe are from amygdala, hippocampus and parahippocampal gyrus, resection of the above structures can contribute in controlling the attack of epilepsy. With respect to the above, anterior temporal lobe unrelated to the occurrence of mesial temporal lobe epilepsy should be resected in anterior temporal lobectomy, as well as most of the hippocampus, amygdala and the parahippocampal structure. Anterior temporal lobectomy has become the standard surgical procedure for the treatment of intractable mesial temporal lobe epilepsy [16], and there were previous reports of about 66% seizure freedom rates [23].

Selective amygdalohippocampectomy is applicable for mesial temporal lobe epilepsy patients accompanied with hippocampal sclerosis [24], and major surgical operation methods include transsylvian [25], transmiddle temporal gyrus [26], subtemporal [27] approach, *etc*. Based on the

results of systematic review and Meta-analysis of patients who received two different surgical treatments postoperatively, Josephson CB *et al*. found that patients who were managed by anterior temporal lobectomy were more likely to achieve Engel Class I as compared to patients managed by selective amygdalohippocampectomy (RR= 1.32, 95% CI, 1.12 to 1.57; $P < 0.01$) [28]. However, there has no distinct conclusion regarding the strengths and weaknesses of anterior temporal lobectomy and selective amygdalohippocampectom in the treatment of epilepsy [28, 29], which should further be verified by multi-center clinical research.

3.1.2. Extratemporal Lobe Epilepsy Resection

Surgical management of extratemporal lobe epilepsy is mainly applicable for patients who had drug-resistant epilepsy induced by cortical dysplasias, accompanied with tumor, ischemic change, and vascular malformation, *etc*. [30]. The incidence of extratemporal lobe epilepsy is mainly from the lateral temporal cortex [31]. A previous retrospective study conducted by Theys T *et al*. has identified the efficacy and safety of surgical treatment for epilepsy in the lateral temporal lobe [32]. The surgical management of extratemporal lobe epilepsy is more common in children due to the prevalence of progressive cortical dysplasia associated with diffuse epileptogenic zones [30, 33]. Epileptogenic zones are often distributed in the cortex, but vary from person to person, and sometimes may reside in the deep structure of the brain. So, an accurate positioning of the epileptogenic zones is a major challenge for the successful implementation of lateral temporal lobe epilepsy surgery [34]. In general, in the premise of ensuring the injury of non-functional areas in the brain, the more thorough the resection of the lesion, the smaller the possibility of recurrence of patients.

3.1.3. Hemispherectomy

Hemispherectomy is predominantly applicable for hemiconvulsions hemiplegia epilepsy syndrome, perinatal injury, unilateral hemispheric cerebral malformations, diffuse cortical dysplasia (such as hemisphere megalencephaly), Rasmussen syndrome and Sturge-Weber syndrome, *etc*. [35]. Major surgical operation methods include anatomical hemispherectomy, functional hemispherectomy, and hemidecortication, *etc*. [36]. Through the study of 83 children with drug-resistant epilepsy, Delalande O *et al*. discovered that about 77% patients achieved the goal of non-relapse of epilepsy(Engel Class I) under the circumstance of non-continuous antiepileptic drugs treatment after hemispherectomy, and 12% of children rarely occurred epilepsy attacks (Engel Class II), and 14% of children indicated a continuous occurrence of epilepsy(Engel Class III or IV) [37], suggesting the efficacy of hemispherectomy in the treatment of drug-resistant epilepsy. Through an average 4.5-years follow-up study, Carlo Efisio Marras *et al*. found 8 of 13 pediatric patients (62%) were seizure free (Engel Class I) after hemispherotomy, and one was classified as Engel Class II, four were Engel Class III or IV [38].

Major complications during the process of excision operation is neurological deficits occurring after surgical resection, including cranial nerve palsy, conscious of visual field defects (hemianopsia) which is not easily perceived by patients, *etc*., but most of the symptoms are temporary [39, 40]. In addition, postoperative complications are more common for surgical resection with a wide range of surgery fields, such as cerebral hemisphere resection. Serious complications may also appear after surgery, including hemiplegia, intracranial infection and intracranial hematoma, brain abscess [41, 42].

3.2. Palliative Surgery

Palliative surgery is a conservative treatment for the treatment of drug-resistant epilepsy, mainly through surgical operation to block the epilepsy discharge diffusion pathway, suitable for epilepsy drug-resistant patients who failed in surgical treatment or patients who are not considered suitable for surgical treatment. Surgical operation methods mainly include corpus callosotomy, multiple subpial transection *etc*. Palliative surgery can reduce or relieve epilepsy seizures to a certain extent.

3.2.1. Corpus Callosotomy

Corpus callosotomy is applicable for patient with multiple epilepsy types, including secondary generalized epilepsy, Lennox–Gastaut syndrome, or Lennox-like syndrome, West syndrome and refractory idiopathic generalized epilepsy, *etc*. [43]. As the largest white matter structure in the human brain, callosum corpus connects the cortex of the two cerebral hemispheres, and callosum corpus fibers play an important role in seizure spread [43, 44]. Callosum corpus is partial or completely dissected in corpus callosotomy, thereby destroying the fiber connections between the two cerebral hemispheres, preventing the focal seizures or the tonic and atonic seizures spread to the opposite side. Seizures in the form of tonic, atonic or mixed epilepsy can cause severe falls (so-called drop seizures). There were previous studies which proved that corpus callosotomy also has a very good therapeutic effect in decreasing seizures [45]. However, the rate of complications after the operation is relatively high, the most classic complications is the disconnection syndrome, and other complications include temporary or permanent motor dysfunctioning, memory and language dysfunctioning [46]. A systematic study on the use of classification Engel by Graham *et al*. observed that total corpus callosotomy had a better curative effect in reducing epilepsy attack as compared to anterior corpus callosotomy (88.2% *vs*. 58.6%, $P < 0.05$) at least 1 year after surgery, the occurrence of disconnection syndrome was significantly higher following total corpus callosotomy than that following anterior corpus callosotomy (12.5% *vs*. 0%; $P < 0.05$) [47].

3.2.2. Multiple Subpial Transection

Multiple subpial transection, originally invented by Morrell in 1989 [48], and continuous improvement was achieved to increase the therapeutic effect, is now mainly used in the following epilepsy types where the epileptogenic zones are observed to be located in language, vision, original motion and sensory function areas, such as Landau Kleffner syndrome (LKS), *etc*. [49, 50]. Epileptic discharge spread is mainly accomplished through the horizontal direction of fibers in the cortical neurons; besides, *via* cutting short fiber in horizontal direction within the cerebral cortex, multiple

subpial transection can protect vertical column, which can contribute to the reservation of the function of functional areas, and can also block the epilepsy discharge pathway, so as to control epilepsy seizures [51]. Through the follow-up of at least 2 years after modified MST operation, Ntsambi-Eba G, *et al*. found that about 79% patients (single MST treatment group, 75%) showed at least 50% decrease of epilepsy attack rate, and 42% patients revealed no epilepsy attack (single MST treatment group, 33%) [52].

3.3. Neurostimulation

Neurostimulation includes vagus nerve stimulation, deep brain stimulation, responsive neurostimulation *etc*.

3.3.1. Vagus Nerve Stimulation

Vagus nerve stimulation was proposed by Zabara in 1985, and in 1988 for the first time, it was applied to the human body [53], which is applicable for drug-resistant epilepsy patients who were unable to remove the lesion and for drug-resistant epilepsy patients with a previous history of surgical treatment failure. The method is to implant the produced electric pulse stimulator in the left chest, and the electrode is connected with the left vagus nerve through the subcutaneous channel to the neck, so as to stimulate the vagus nerve to control epilepsy attack [54], vagus nerve stimulation has been approved by the U.S. FDA in 1997, as an adjuvant therapy for drug-resistant epilepsy [55]. The antiepileptic mechanism of Vagus Nerve Stimulation is still not understood sufficiently, and some studies have speculated that it may be associated with brainstem nuclei [56]. Nucleus of the solitary tract (NTS), which is the main terminal point, has direct or indirect projections to the raphe nuclei, locus coeruleus, reticular formation, and other brainstem nuclei. These nuclei have been confirmed to affect the cerebral seizure susceptibility, thereby, vagal modulation of these nuclei could represent the mechanism for seizure-attenuating [57]. Krahl *et al*. demonstrated that the locus coeruleus plays a crucial role in suppressing epilepsy of VNS in rat models [58]. In addition, $GABA_A$ receptor density, the immunomodulatory function of the vagus nerve, noradrenaline and serotonin could contribute to the seizure attenuating effects of VNS [59-61]. The earliest trial of the vagus nerve stimulation is reported to be applied for refractory epilepsy patients in the early 1990s [62]. Englot DJ *et al*. found through Meta analysis that following vagus nerve stimulation, the frequency of epilepsy seizures reduced to over 50% (OR = 1.83 95%CI 1.80-1.86) [63]. By a 5-year follow-up study of drug-resistant epilepsy patients who are managed by vagus nerve stimulation, Pakdaman H *et al*. found that overall mean frequency of monthly seizures decreased by 57.8-67%, which confirmed the safety and effectiveness [64]. Vagus nerve stimulation has fewer side effects, and the incidence rate is about 2%, mainly including hoarse voice and cough, postoperative hematoma, and infection, *etc*. [65]. But the vagus nerve stimulation is currently only used as an adjuvant therapy for drug-resistant epilepsy, rarely able to completely prevent the onset of epilepsy. At the same time, the current vagus nerve stimulation is an invasive treatment, and requires a second surgery per 5-10 years to complete the replacement of the battery, which is likely to cause the emergence of complications again. Furthermore, vagus nerve stimulator can not get effective imaging observation by MRI, which is a challenge for the wide application in clinic in future. At present, transcutaneous vagus nerve stimulation (tVNS) is gradually rised and has been proved to be safe and effective in the treatment of epilepsy. Through a double blind randomized controlled trial, Bauer S found that transcutaneous auricular vagus nerve stimulation (ta-VNS), as a non-invasive technique, has a high treatment compliance and tolerability, and compared with the control group, patients in the 25 Hz treatment group indicated a significant decrease regarding the frequency of epilepsy seizures (20 weeks; n = 26, 34.2%, $P = 0.034$) [66]. Rong P *et al*. found in their research that in comparison of ta-VNS treated patients and the controls, the frequency of epilepsy seizures reduction in the former group was significantly higher than the latter group after 8 weeks of treatment (42.6% vs. 11.5%, $P < 0.05$) [67]. Although, ta-VNS has been proven to be effective in the treatment of drug-resistant epilepsy, more basic and clinical studies are needed to provide further supports and guidance for the clinical application of the technology.

3.3.2. Deep Brain Stimulation

Deep brain stimulation has been involved in the therapeutic test for the treatment of drug-resistant epilepsy since 1950s, and targets for the deep brain stimulation in the treatment of epilepsy include centromedian nucleus of the thalamus, anterior nucleus of the thalamus, subthalamic nucleus, hippocampus, locus coeruleus, *etc*., yet the antiepileptic mechanism of deep brain stimulation still remains unclear. A multi-center double blind RCT regarding anterior thalamic nucleus stimulation suggested that a 56% median percent reduction in seizure frequency and 54% of patients had a seizure reduction of at least 50% [68]. Thalamic deep brain stimulation has been approved in the European Union, Canada and other countries as an adjunctive therapy for drug-resistant epilepsy and secondary generalized seizures, but still not approved by U.S. FDA [69]. Most common complications include bleeding, infection, mechanical complications, neuropsychiatric changes, but death and serious complications are rare [70]. Although deep brain stimulation in the treatment of anterior nucleus of the thalamus and hippocampus has been demonstrated through a large number of RCTs, however, further research is needed to confirm therapeutic effects of other targets.

3.3.3. Responsive Neurostimulation

Responsive neurostimulation is applicable for the treatment of refractory focal epilepsy patients who have failed in a variety of treatment modalities [71]. Responsive neurostimulation is a new technology that can discover epilepsy seizure activities in the brain through monitoring electrocorticographic activity, and to give a direct focal electrical stimulation, so as to reduce epilepsy seizure through the targeted way [72]. Responsive neurostimulation can precisely suppress the γ band (35-100 Hz) phase locking to suppress the epileptiform activity, and separate the stimulation region from the downstream target [73]. Through target area electrode placement in the brain, it is connected with the analysis

device placed subcutaneously, which can achieve continuous recording neural physiological signals in the target area of the brain, and can support data analysis with the self-taking program, to give appropriate stimulus processing. Hence the advantage of this device is the effective combination of seizure activities monitoring and electrical stimulation,. Morrell MJ *et al*. have found that 12 weeks after implantation, frequency of seizures were significantly deceased in the treatment (-37.9% n =97) compared to the sham group (-17.3% n =94; p =0.012) and there was no significant difference found between two groups regarding the adverse events, which approved the effectiveness of responsive neurostimulation in the treatment of epilepsy [71]. However, to date, the method is limited [74], and more RCT researches are needed to make the method widely used in clinical applications.

3.4. Other Surgical Interventions

3.4.1. Stereotactic Radiosurgery

In the recent years, the non-invasive radiation therapy has been applied for the control of epilepsy. By focusing on the ionizing radiation targeted to the deep lesions, this method can avoid the damage to the surrounding tissue. The photon accelerator is the most widely used in ionizing radiation, such as cyber knife, gamma knife *etc*. Mainly through the neuromodulation mechanism, stereotactic radiosurgery can contribute to the reduction of both excitatory neurotransmitter and inhibitory neurotransmitter, or through ischemic necrosis of epileptic tissue to isolate and destruct connection between the middle neuron and to block the conduction of the epileptic attack, to achieve the purpose of reducing the occurrence of seizures or changing the form of seizures and protecting the brain function [75]. The main advantage of stereotactic radiosurgery lies in the non-invasive treatment, without the need for craniotomy and other surgical procedures to complete the treatment of deep lesions and multiple lesions, so as to avoid the inherent brain tissue traction or injury, but require higher precise positioning. The disadvantage is that the curative effect of stereotactic radiosurgery is delayed to decrease the frequency of epilepsy attack, Chang EF *et al*. have shown in their study that an epilepsy remission occurred later in patients treated by stereotactic radiosurgery [76]. And during this period, epilepsy attacks still occur, and the risk associated with the incidence of epilepsy and mortality remains. In addition, there is a secondary injury and delayed malignancy that is secondary to radiation. Stereotactic radiosurgery is an open surgical operation for the treatment of drug-resistant epilepsy, the antiepileptic mechanism still remains unclear. It was first discovered that its antiepileptic effect was in the treatment of the tumor, such as tumors, Arteriovenous Malformations (AVMs), cavernous malformations (CMs) and hypothalamic hamartoma (HHs), *etc*., which is the most obvious especially in the treatment of arteriovenous malformations associated with epilepsy. During the median 65.6-months follow-up period, Przybylowski CJ *et al*. found that a sum up of 65 cases of patients (89%) achieved seizure remission in altogether 73 cases of epilepsy patients before SAR, and there were 21 cases of patients (33%) who reduced the usage of antiepileptic drugs in the 63 cases of patients before surgery (P = 0.05) [77], suggesting that stereotactic radiosurgery may be effective for the control of long-term arteriovenous malformations associated epilepsy seizures.

3.4.2. Stereotactic Laser Ablation (SLA)

When the epileptogenic zone is located in the deep brain or the important structure of the brain, which is not suitable to do the surgery, the stereotactic laser ablation may be a good choice [78]. The stereotactic laser ablation procedure can be performed with a small scalp incision and miniature burr hole, with a laser probe which is placed using a stereotactic frame or interventional MRI technique [79]. By locating and destroying the epileptogenic zone, SLA can inhibit the abnormal electrical activity of neurons in the epilepsy, and destroying the conduction pathway of epilepsy activity, blocking the spread of epileptic discharge to the surrounding cortex, thereby controlling the epilepsy attack. Lewis EC *et al*. conducted their study by involving 17 cases of postoperative patients managed by nuclear magnetic guided laser interstitial thermal therapy and found that seven patients (41%) achieved Engel class I outcome, and one of the seventeen patients (6%) achieved Engel class II outcome, Engel class III in three of 17 the patients (18%), and Engel class IV in six (35%) [80]. By observing the epilepsy attack in 20 cases of patients following laser interstitial thermal therapy, Kang JY *et al*. found that 8 of 15 patients (53%, 95% CI 30.1-75.2%) were free of seizures after 6 months postoperative, 4 of 11 patients (36.4%, 95% CI 14.9-64.8%) were free of seizures after 1 year, and 3 of 5 patients (60%, 95% CI 22.9-88.4%) were free of seizures at 2-year follow-up [81]. These studies have demonstrated the efficacy and safety of SLA in the treatment of drug-resistant epilepsy, but more basic and clinical studies are needed to be carried out in future.

The time for surgery is especially crucial due to complexity and progressivity of epilepsy. For children with drug-resistant epilepsy, early surgery may obtain a better outcome because children have greater plasticity and ability to reorganize functions in the developing brain compared to a more mature brain. A large scale of researches has confirmed. Chugani HT *et al*. reviewed from 65 (33 male) patients with epileptic spasms who underwent surgery and found that in 34 patients operated <3 years after seizure onset, 30 (88%) achieved class I outcome that is higher than average success rates (71%), which indirectly demonstrate curative epilepsy surgery in epileptic spasms patients, with or without history of infantile spasms, is best accomplished at an early age [82]. Anita Althausen *et al*. divided 61 patients into three groups (early:<7 years/intermediate: 7–16 years/late: >16 years) and found that best seizure outcome was obtained for early surgery patients (90% seizure free) through a long-term outcome followed-up hemispheric surgery, [83]. For adults with drug-resistant epilepsy, who are suitable for surgery, it seems that performing a surgery as soon as possible is beneficial. However, a correlation between outcome after surgery and time for surgery is moderate. And the best time for surgery remains to be explored.

3.5. Adjuvant Therapy with Antiepileptic Drugs in the Perioperative Period

Seizure freedom and without further needs of continuous application of antiepileptic drugs are surely the most desir-

able outcome in patients with drug-resistant epilepsy postoperatively. But in most cases, simple surgery does not completely control the onset of epilepsy. Perioperative drug therapy is also critical, and is currently the most important part of the comprehensive therapy targeting drug-resistant epilepsy. The cure of epilepsy after operation is not only related to the completion degree of surgical resection, but also related to perioperative medication strategy. Usually, antiepileptic drugs should be used for one to two years in patients with epilepsy postoperatively, or even indefinite [84].

Levetiracetam (LEV) is a new type of antiepileptic drugs, by inhibiting the N type calcium current in the CA1 region of the hippocampus [85], reducing zinc ion and β-carbolines mediated GABA- and glycine-gated current, affecting the function of GABA receptor, thereby exerting antiepileptic roles [86]. Currently, the drug is mainly applied for first-line treatment of generalized tonic clonic seizures, myoclonic seizures and focal seizures. Jehi *et al*. found in their study showing that in the perioperative period of temporal lobectomy, patients of the LEV administration group revealed a relatively lower frequency of epilepsy seizure postoperatively (RR=0.62, 95% CI 0.43-0.89, RR = 0.57, 95% CI 0.39-0.83) [87], suggesting that there existed possibility of LEV in the postoperative antiepileptic treatment. However, a retrospective analysis of clinical data of 106 cases of epilepsy patients receiving resection surgery was made, Ramsekhar Menon *et al*. attempted AED withdrawal in 94 cases of patients (88.7%). Following withdrawal, it was found that there were 44 cases of patients (41.5%) who showed another relapse of epilepsy due to the decreased administration of antiepileptic drugs, among which seizure-free did not occur subsequently in about 14 cases of patients (31.8%), besides, the one-third recurrence patients failed to control the occurrence of seizures upon AEDs reintroduction [88]. By performing the withdrawal of antiepileptic drugs in 223 cases of postoperative patients, Park *et al*. conducted antiepileptic drugs reduction processing in 147 cases of patients (65.9%) and found that a total of 78 cases of patients (53.1%) indicated a relapse of epilepsy after initial reduction. The phenomenon of antiepileptic drug termination was detected in a sum up of 73 cases of patients (32.7%), among which 59 cases of patients (80.8%) were seizure free even once until final assessment [89].

Although antiepileptic drugs are of great significance in postoperative consolidation therapy and reducing the recurrence of epilepsy, there are no clear standards for the perioperative treatment of drug-resistant epilepsy. How to use and terminate, and when to terminate drugs and other issues still exist along with great controversy in patients with drug-resistant epilepsy in the perioperative period when using antiepileptic drugs [84], which needs to be further explored on the basis of further basic and clinical researches.

3.6. Expectation

As for drug-resistant epilepsy, accurate surgical resection has more important significance for the complete or incomplete free of seizure, accurate preoperative localization can not only contribute to the reduction of the risk of surgery, but also help to develop a perfect operation strategy, which can also have a significant impact on the reduction of postoperative complications and improvement of prognostic outcomes. Therefore, it is very important to accurately locate the epileptogenic zone and the functional areas of the brain.

While preoperative assessment of new technologies is emerging, the role of EEG in clinical trials is still irreplaceable because it can describe the onset and progression of a specific description of epilepsy in time domain. Since the promotion of stereoelectroencephalography (SEEG) by Bancaud and Talairach in 1970s, it has been used for the preoperative location and evaluation of epilepsy, and achieved great success [90]. Magnetic resonance imaging of epilepsy provides an intuitive and clear anatomical image for the etiological diagnosis of epilepsy. It has been widely used in the preoperative localization of epilepsy. At present, structural MRI is still the main neuro imaging technology for localization of epileptogenic zone. However, 15 - 30% patients with drug-resistant epilepsy lesions did not have an obvious lesion on the MRI (for example, they were MRI negative) [91, 92], which greatly limits the effective application of MRI technology. Recently, the emerging of functional MRI and magnetic resonance spectroscopy provides new development for the application of magnetic resonance technology. Functional MRI is based on the application of blood oxygen level dependent technique to detect the changes of cerebral blood flow dynamics, and it could be used to locate the epileptogenic zones or the functional areas related to language, motor function, memory and so on [93]. On the other hand, relied on the combination techniques of magneto encephalography (MEG) and MRI data, magnetic resonance spectroscopy can lead to a relative quantitative analysis for *in vivo* brain biochemical substances concentrations, which may contribute to the direct reflection of changes in the metabolism of nerve cells, which thus leads to the indirect confirmation pathological changes of lesions, which is especially sensitive in temporal lobe epilepsy localization [94]. At the same time, along with the development of nuclear medicine technology, ^{18}F-FDG (^{18}F-fluorodeoxyglucose) PET and ictal SPECT has also been used in the evaluation of epilepsy surgery. The main advantages of clinical PET imaging are not only reflecting the progress of the blood flow of the tracer in the body including perfusion and metabolism, but also quantitatively reflecting the distribution of radioactive markers. And in the epileptogenic region of ictal SPECT, there was an area of hypoperfusion, which might be caused by blood flow shifting to the epileptogenic zone or might represent an inhibitory zone that limits the spread of seizure, thereby resulting in locating lesion of the epilepsy [95]. M. Goodfellow *et al*. used mathematical models to simulate recurrent pathological dynamics and quantify global (whole brain) and local (brain regions) ictogenicity based on preoperative ECoG data of epilepsy patients, which provide a promising prospect for preoperative assessment and postoperative prediction of drug-resistant epilepsy [96]. At the same time, several techniques have been developed to map the source of interictal epileptiform discharges (IEDs), including electroencephalography-functional (EEG-fMRI), electroencephalography source imaging (ESI), and magnetic source imaging (MSI), and has made great progress [97, 98].

With the continuous development of science and technology, preoperative evaluation and location method of epilepsy will be perfected to continue to improve the accuracy of lesion localization, also contribute to a wild application perspective for comprehensive treatment mainly based on surgery.

As an important portion of adjuvant therapy for drug-resistant epilepsy, drug therapy plays an irreplaceable role in the treatment of epilepsy. Recently, some promising drugs targets have been emerging gradually, which provides some novel possibilities and potential biochemical indicators for clinical evaluation in the management of epilepsy in future. Glutamate neurotransmitters and Ca^{2+} channels are known to play an important role in the etiology of epilepsy [99-101]. TRPV1 is a non-selective channel with high Ca^{2+} permeability, and synaptic terminals whose activation typically facilitates glutamate release through increased excitability of neurons [102]. There are two main TRPV1 channel blockers, namely capsazepine (CPZ) and resiniferatoxin, which have been reported on anticonvulsant roles [103]. Thus, targeting the TRPV1 channel activity may provide a feasible strategy for treatment of drug-resistant epilepsy. Na^+ K^+ $2Cl^-$ co-transporter (NKCC) belongs to cation-dependent chloride co-transporter family and induces transport of Na^+, K^+ and Cl^- ions into the cell [104]. Activation of NKCC allows the entry of Na^+, K^+ and $2Cl^-$ inside the cell, and that roles of the NKCC1 blocker (bumetanide) about decreased the Cl^- accumulation, suppressed epileptiform activity in neonatal rats have been proved [105]. Sen *et al*. also confirmed the increased expression of NKCC1 in medically resistant refractory human epilepsy with hippocampal sclerosis and focal cortical dysplasia [106]. Although some reports have demonstrated potential of NKCC1 blocker for drug-resistant epilepsy treatment, more studies are still required to explore. Enhanced gap junctional communication between neurons may be an underlying factor related to the generation of epilepsy [107]. Some chemical compounds, such as Carbenoxolone, mefloquine, quinine, quinidine *et al*. characterized as gap junction blockers have been evaluated on animal seizure models, which can be an underlying possibility for development of antiepileptic drug [108]. There is an experimental evidence indicating that oxidative stress may be involved in the epileptogenesis of epilepsy [109], providing possibility for Selenium as a potential drug to treat epilepsy due to its inoxidizability [110]. Savaskan NE *et al*. have shown that Selenium deficiency may lead to increased susceptibility to glutamate-induced excitotoxicity. Undoubtedly, a mass of clinical studies needs to be continued. Recent advances in studies on interacting proteins of neurotransmitter receptor systems suggest that agonists or antagonists of mGluRs, especially group I mGluR antagonists are promising candidate drugs to control seizures and subsequent neurodegeneration. And different receptor systems may share the common signal transduction pathways or interacting proteins, which may provide therapeutic targets for pharmaceutical treatment of epilepsy [111].

In addition to drug therapy, the ketogenic diet, Chinese medicine therapy and immunotherapy are also effective adjuvant therapy for drug-resistant epilepsy. Ketogenic diet is a high fat, low carbohydrate and appropriate protein diet therapy, applicable for all age groups of children with drug-resistant epilepsy [112]. This therapy may inhibit the onset of epilepsy by interrupting the glutaminergic synaptic transmission, inhibiting the activation of the ATP sensitive potassium channel and the $GABA_B$ receptor and enhancing the GABA mediated inhibition [113]. Through the study of 1-18 years old children and adolescents with drug-resistant epilepsy, Lambrechts *et al*. observed that the frequency of epilepsy seizure in ketogenic diet treatment group was significantly lower than that in the care as in usual group, providing class I evidence that ketogenic diet may be effective therapeutic method for the treatment of drug-resistant epilepsy in children and adolescents [114].

Drug-resistant epilepsy is referred to as refractory epilepsy in the traditional Chinese medicine, the disease course is long accompanied with progressive deterioration. In the past few thousand years, plant extracts and herbs are often used in the treatment of individuals with epilepsy seizures, and in many cases are considered to be safe [115, 116]. A large number of clinical and experimental studies have confirmed antiepileptic effects of compound prescriptions, such as saiko-ka-ryukotsu-borei-to and Epilepsy tablets [117, 118]. Immunotherapy is also a new adjuvant therapy for drug-resistant epilepsy. Currently available options for the treatment of epilepsy include steroids (corticosteroids, glucocorticoids), plasmapheresis, intravenous immunoglobulin, steroid-sparing drugs such as azathioprine and so on [119]. Immunotherapy can effectively avoid side effects of antiepileptic drugs, and also prevent traumatic brain injury, stroke, intracranial infection through the addressing of inflammation in patients at high risk for epilepsy seizure. However, the relevant mechanism of immunotherapy is not completely clear, and the cost of treatment is high, above which are the problems that need to be solved in a wide range of applications.

With the development of genomic and genetic research, cell transplantation and gene therapy have been gradually acknowledged by people as potential antiepileptic therapies. Gene therapy has been shown to inhibit the local neocortical epilepsy seizure in a rodent model [120], and breakthrough progress has been made in animal experiments [121]. Targets of gene research include galanin (GAL) and neuropeptide Y (NPY), *etc*. Relevant study indicated that NPY was widely expressed in the brain and can reduce chronic spontaneous seizures in temporal lobe epilepsy mice models [122]. Overexpression of recombinant adeno-associated viral (rAAV) vector mediated endogenous polypeptide in the hippocampus can exert long-term effect of decreasing epilepsy seizure in a variety of animal models [122-124]. However, the treatment efficacy of gene therapy and cell transplantation needs to be verified in a large number of animals and clinical trials.

CONCLUSION

Above mentioned therapies are the adjuvant therapies of drug-resistant epilepsy, we look forward to see more clinical studies combining these methods with the standard surgical treatment, further promoting new exploration of antiepileptic comprehensive treatment mainly based on surgery, so as to

achieve the remission and even cure of drug-resistant epilepsy with the development of the epileptogenic zone localization and imaging technology, as well as the deepening of drug-resistant epilepsy mechanism researches, comprehensive treatment mainly based on surgery will continue to be improved and popularized, and finally bring a new dawn for drug-resistant epilepsy patients.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Fisher, R.S.; Acevedo, C.; Arzimanoglou, A.; Bogacz, A.; Cross, J.H.; Elger, C.E.; Engel, J., Jr; Forsgren, L.; French, J.A.; Glynn, M.; Hesdorffer, D.C.; Lee, B.I.; Mathern, G.W.; Moshé, S.L.; Perucca, E.; Scheffer, I.E.; Tomson, T.; Watanabe, M.; Wiebe, S. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia,* **2014**, *55*(4), 475-482. [http://dx.doi.org/10.1111/epi.12550] [PMID: 24730690]

[2] Murray, G.J. L.A. Global Comparative Assessments in the Health Sector: Disease Burden, Expenditure, Intervention Packages, **1994**.

[3] Kwan, P.; Brodie, M.J. Early identification of refractory epilepsy. *N. Engl. J. Med.,* **2000**, *342*(5), 314-319. [http://dx.doi.org/10.1056/NEJM200002033420503] [PMID: 10660394]

[4] Kwan, P.; Arzimanoglou, A.; Berg, A.T.; Brodie, M.J.; Allen H.W.; Mathern, G.; Moshé, S.L.; Perucca, E.; Wiebe, S.; French, J. Definition of drug resistant epilepsy: consensus proposal by the ad hoc task force of the ILAE commission on therapeutic strategies. *Epilepsia,* **2010**, *51*(6), 1069-1077. [http://dx.doi.org/10.1111/j.1528-1167.2009.02397.x] [PMID: 19889013]

[5] Löscher, W.; Luna-Tortós, C.; Römermann, K.; Fedrowitz, M. Do ATP-binding cassette transporters cause pharmacoresistance in epilepsy? Problems and approaches in determining which antiepileptic drugs are affected. *Curr. Pharm. Des.,* **2011**, *17*(26), 2808-2828. [http://dx.doi.org/10.2174/138161211797440212] [PMID: 21827408]

[6] Margineanu, D.G.; Klitgaard, H. Mechanisms of drug resistance in epilepsy: relevance for antiepileptic drug discovery. *Expert Opin. Drug Discov.,* **2009**, *4*(1), 23-32. [http://dx.doi.org/10.1517/17460440802611729] [PMID: 23480334]

[7] Salvamoser, J.D.; Avemary, J.; Luna-Munguia, H.; Pascher, B.; Getzinger, T.; Pieper, T.; Kudernatsch, M.; Kluger, G.; Potschka, H. Glutamate-mediated down-regulation of the multidrug-resistance protein BCRP/ABCG2 in porcine and human brain capillaries. *Mol. Pharm.,* **2015**, *12*(6), 2049-2060. [http://dx.doi.org/10.1021/mp500841w] [PMID: 25898179]

[8] Remy, S.; Beck, H. Molecular and cellular mechanisms of pharmacoresistance in epilepsy. *Brain,* **2006**, *129*(Pt 1), 18-35. [http://dx.doi.org/10.1093/brain/awh682] [PMID: 16317026]

[9] Löscher, W.; Potschka, H. Drug resistance in brain diseases and the role of drug efflux transporters. *Nat. Rev. Neurosci.,* **2005**, *6*(8), 591-602. [http://dx.doi.org/10.1038/nrn1728] [PMID: 16025095]

[10] Römermann, K.; Helmer, R.; Löscher, W. The antiepileptic drug lamotrigine is a substrate of mouse and human breast cancer resistance protein (ABCG2). *Neuropharmacology,* **2015**, *93*, 7-14. [http://dx.doi.org/10.1016/j.neuropharm.2015.01.015] [PMID: 25645391]

[11] Koubeissi, M. Neuropathology of the blood-brain barrier in epilepsy: support to the transport hypothesis of pharmacoresistance. *Epilepsy Curr.,* **2013**, *13*(4), 169-171. [http://dx.doi.org/10.5698/1535-7597-13.4.169] [PMID: 24009480]

[12] Rogawski, M.A.; Löscher, W. The neurobiology of antiepileptic drugs. *Nat. Rev. Neurosci.,* **2004**, *5*(7), 553-564. [http://dx.doi.org/10.1038/nrn1430] [PMID: 15208697]

[13] Møller, R.S.; Schneider, L.M.; Hansen, C.P.; Bugge, M.; Ullmann, R.; Tommerup, N.; Tümer, Z. Balanced translocation in a patient with severe myoclonic epilepsy of infancy disrupts the sodium channel gene SCN1A. *Epilepsia,* **2008**, *49*(6), 1091-1094. [http://dx.doi.org/10.1111/j.1528-1167.2008.01550.x] [PMID: 18294202]

[14] Yu, F.H.; Mantegazza, M.; Westenbroek, R.E.; Robbins, C.A.; Kalume, F.; Burton, K.A.; Spain, W.J.; McKnight, G.S.; Scheuer, T.; Catterall, W.A. Reduced sodium current in GABAergic interneurons in a mouse model of severe myoclonic epilepsy in infancy. *Nat. Neurosci.,* **2006**, *9*(9), 1142-1149. [http://dx.doi.org/10.1038/nn1754] [PMID: 16921370]

[15] Escayg, A.; Heils, A.; MacDonald, B.T.; Haug, K.; Sander, T.; Meisler, M.H. A novel SCN1A mutation associated with generalized epilepsy with febrile seizures plus--and prevalence of variants in patients with epilepsy. *Am. J. Hum. Genet.,* **2001**, *68*(4), 866-873. [http://dx.doi.org/10.1086/319524] [PMID: 11254445]

[16] Wiebe, S.; Blume, W.T.; Girvin, J.P.; Eliasziw, M. A randomized, controlled trial of surgery for temporal-lobe epilepsy. *N. Engl. J. Med.,* **2001**, *345*(5), 311-318. [http://dx.doi.org/10.1056/NEJM200108023450501] [PMID: 11484687]

[17] Fiest, K.M.; Sajobi, T.T.; Wiebe, S. Epilepsy surgery and meaningful improvements in quality of life: results from a randomized controlled trial. *Epilepsia,* **2014**, *55*(6), 886-892. [http://dx.doi.org/10.1111/epi.12625] [PMID: 24735200]

[18] Jallon, P.; Loiseau, P.; Loiseau, J. Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Coordination Active du Réseau Observatoire Longitudinal de l' Epilepsie. *Epilepsia,* **2001**, *42*(4), 464-475. [http://dx.doi.org/10.1046/j.1528-1157.2001.31400.x] [PMID: 11440341]

[19] Engel, J., Jr; Wiebe, S.; French, J.; Sperling, M.; Williamson, P.; Spencer, D.; Gumnit, R.; Zahn, C.; Westbrook, E.; Enos, B. Practice parameter: temporal lobe and localized neocortical resections for epilepsy: report of the quality standards subcommittee of the american academy of neurology, in association with the american epilepsy society and the american association of neurological surgeons. *Neurology,* **2003**, *60*(4), 538-547. [http://dx.doi.org/10.1212/01.WNL.0000055086.35806.2D] [PMID: 12601090]

[20] Engel, J., Jr; McDermott, M.P.; Wiebe, S.; Langfitt, J.T.; Stern, J.M.; Dewar, S.; Sperling, M.R.; Gardiner, I.; Erba, G.; Fried, I.; Jacobs, M.; Vinters, H.V.; Mintzer, S.; Kieburtz, K. Early surgical therapy for drug-resistant temporal lobe epilepsy: a randomized trial. *JAMA,* **2012**, *307*(9), 922-930. [http://dx.doi.org/10.1001/jama.2012.220] [PMID: 22396514]

[21] de Tisi, J.; Bell, G.S.; Peacock, J.L.; McEvoy, A.W.; Harkness, W.F.; Sander, J.W.; Duncan, J.S. The long-term outcome of adult epilepsy surgery, patterns of seizure remission, and relapse: a cohort study. *Lancet,* **2011**, *378*(9800), 1388-1395. [http://dx.doi.org/10.1016/S0140-6736(11)60890-8] [PMID: 22000136]

[22] Joo, E.Y.; Han, H.J.; Lee, E.K.; Choi, S.; Jin, J.H.; Kim, J.H.; Tae, W.S.; Seo, D.W.; Hong, S.C.; Lee, M.; Hong, S.B. Resection extent versus postoperative outcomes of seizure and memory in mesial temporal lobe epilepsy. *Seizure,* **2005**, *14*(8), 541-551. [http://dx.doi.org/10.1016/j.seizure.2005.08.011] [PMID: 16242970]

[23] Hu, W.H.; Zhang, C.; Zhang, K.; Meng, F.G.; Chen, N.; Zhang, J.G. Selective amygdalohippocampectomy versus anterior temporal lobectomy in the management of mesial temporal lobe epilepsy: a meta-analysis of comparative studies. *J. Neurosurg.*, **2013**, *119*(5), 1089-1097.

[24] Hoyt, A.T.; Smith, K.A. Selective Amygdalohippocampectomy. *Neurosurg. Clin. N. Am.,* **2016**, *27*(1), 1-17. [http://dx.doi.org/10.1016/j.nec.2015.08.009] [PMID: 26615103]

[25] Adada, B. Selective amygdalohippocampectomy via the transsylvian approach. *Neurosurg. Focus,* **2008**, *25*(3), E5. [http://dx.doi.org/10.3171/FOC/2008/25/9/E5] [PMID: 18759629]

[26] Wheatley, B.M. Selective amygdalohippocampectomy: the trans-middle temporal gyrus approach. *Neurosurg. Focus,* **2008**, *25*(3), E4. [http://dx.doi.org/10.3171/FOC/2008/25/9/E4] [PMID: 18759628]

[27] Sajko, T.; Skoro, I.; Rotim, K. How I do it - selective amygdalohippocampectomy *via* subtemporal approach. *Acta Neurochir. (Wien),* **2013**, *155*(12), 2381-2387. [http://dx.doi.org/10.1007/s00701-013-1846-2] [PMID: 23989995]

[28] Josephson, C.B.; Dykeman, J.; Fiest, K.M.; Liu, X.; Sadler, R.M.; Jette, N.; Wiebe, S. Systematic review and meta-analysis of standard *vs*. selective temporal lobe epilepsy surgery. *Neurology,* **2013**, *80*(18), 1669-1676. [http://dx.doi.org/10.1212/WNL.0b013e3182904f82] [PMID: 23553475]

[29] Hu, W.H.; Zhang, C.; Zhang, K.; Meng, F.G.; Chen, N.; Zhang, J.G. Selective amygdalohippocampectomy versus anterior temporal lobectomy in the management of mesial temporal lobe epilepsy: a meta-analysis of comparative studies. *J. Neurosurg.,* **2013**, *119*(5), 1089-1097. [http://dx.doi.org/10.3171/2013.8.JNS121854] [PMID: 24032705]

[30] Prayson, R.A.; Frater, J.L. Cortical dysplasia in extratemporal lobe intractable epilepsy: a study of 52 cases. *Ann. Diagn. Pathol.,* **2003**, *7*(3), 139-146. [http://dx.doi.org/10.1016/S1092-9134(03)00010-8] [PMID: 12808564]

[31] Englot, D.J.; Wang, D.D.; Rolston, J.D.; Shih, T.T.; Chang, E.F. Rates and predictors of long-term seizure freedom after frontal lobe epilepsy surgery: a systematic review and meta-analysis. *J. Neurosurg.,* **2012**, *116*(5), 1042-1048. [http://dx.doi.org/10.3171/2012.1.JNS111620] [PMID: 22304450]

[32] Theys, T. Mesial extratemporal lobe epilepsy: Clinical features and surgical strategies. *Neurosurgery,* **2016**. [http://dx.doi.org/10.1227/NEU.0000000000001230] [PMID: 28173579]

[33] Frater, J.L.; Prayson, R.A.; Morris, H.H., III; Bingaman, W.E. Surgical pathologic findings of extratemporal-based intractable epilepsy: a study of 133 consecutive resections. *Arch. Pathol. Lab. Med.,* **2000**, *124*(4), 545-549. [PMID: 10747311]

[34] Roper, S.N. Surgical treatment of the extratemporal epilepsies. *Epilepsia,* **2009**, *50*(Suppl. 8), 69-74. [http://dx.doi.org/10.1111/j.1528-1167.2009.02239.x] [PMID: 19702737]

[35] Granata, T.; Matricardi, S.; Ragona, F.; Freri, E.; Casazza, M.; Villani, F.; Deleo, F.; Tringali, G.; Gobbi, G.; Tassi, L.; Lo Russo, G.; Marras, C.E.; Specchio, N.; Vigevano, F.; Fusco, L. Hemispherotomy in Rasmussen encephalitis: long-term outcome in an Italian series of 16 patients. *Epilepsy Res.,* **2014**, *108*(6), 1106-1119. [http://dx.doi.org/10.1016/j.eplepsyres.2014.03.018] [PMID: 24815913]

[36] Pinto, A.L.; Lohani, S.; Bergin, A.M.; Bourgeois, B.F.; Black, P.M.; Prabhu, S.P.; Madsen, J.R.; Takeoka, M.; Poduri, A. Surgery for intractable epilepsy due to unilateral brain disease: a retrospective study comparing hemispherectomy techniques. *Pediatr. Neurol.,* **2014**, *51*(3), 336-343. [http://dx.doi.org/10.1016/j.pediatrneurol.2014.05.018] [PMID: 25160539]

[37] Delalande, O. Vertical parasagittal hemispherotomy: surgical procedures and clinical long-term outcomes in a population of 83 children. *Neurosurgery,* **2007**, *60*(2 Suppl 1), p. ONS19-32; discussion ONS32.

[38] Marras, C.E.; Granata, T.; Franzini, A.; Freri, E.; Villani, F.; Casazza, M.; De Curtis, M.; Ragona, F.; Ferroli, P.; D'Incerti, L.; Pincherle, A.; Spreafico, R.; Broggi, G. Hemispherotomy and functional hemispherectomy: indications and outcome. *Epilepsy Res.,* **2010**, *89*(1), 104-112. [http://dx.doi.org/10.1016/j.eplepsyres.2009.09.006] [PMID: 19883995]

[39] Hader, W.J.; Tellez-Zenteno, J.; Metcalfe, A.; Hernandez-Ronquillo, L.; Wiebe, S.; Kwon, C.S.; Jette, N. Complications of epilepsy surgery: a systematic review of focal surgical resections and invasive EEG monitoring. *Epilepsia,* **2013**, *54*(5), 840-847. [http://dx.doi.org/10.1111/epi.12161] [PMID: 23551133]

[40] Delev, D. Vision after trans-sylvian or temporobasal selective amygdalohip-pocampectomy: a prospective randomised trial. *Acta Neurochir (Wien),* **2016**, *158*(9), 1757-65.

[41] Griessenauer, C.J.; Salam, S.; Hendrix, P.; Patel, D.M.; Tubbs, R.S.; Blount, J.P.; Winkler, P.A. Hemispherectomy for treatment of refractory epilepsy in the pediatric age group: a systematic review. *J. Neurosurg. Pediatr.,* **2015**, *15*(1), 34-44. [http://dx.doi.org/10.3171/2014.10.PEDS14155] [PMID: 25380174]

[42] Tebo, C.C.; Evins, A.I.; Christos, P.J.; Kwon, J.; Schwartz, T.H. Evolution of cranial epilepsy surgery complication rates: a 32-year systematic review and meta-analysis. *J. Neurosurg.,* **2014**, *120*(6), 1415-1427. [http://dx.doi.org/10.3171/2014.1.JNS131694] [PMID: 24559222]

[43] Unterberger, I.; Bauer, R.; Walser, G.; Bauer, G. Corpus callosum and epilepsies. *Seizure,* **2016**, *37*, 55-60. [http://dx.doi.org/10.1016/j.seizure.2016.02.012] [PMID: 27010176]

[44] van der Knaap, L.J.; van der Ham, I.J. How does the corpus callosum mediate interhemispheric transfer? A review. *Behav. Brain Res.,* **2011**, *223*(1), 211-221. [http://dx.doi.org/10.1016/j.bbr.2011.04.018] [PMID: 21530590]

[45] Bower, R.S.; Wirrell, E.; Nwojo, M.; Wetjen, N.M.; Marsh, W.R.; Meyer, F.B. Seizure outcomes after corpus callosotomy for drop attacks. *Neurosurgery,* **2013**, *73*(6), 993-1000. [http://dx.doi.org/10.1227/NEU.0000000000000161] [PMID: 24030172]

[46] Jea, A.; Vachhrajani, S.; Widjaja, E.; Nilsson, D.; Raybaud, C.; Shroff, M.; Rutka, J.T. Corpus callosotomy in children and the disconnection syndromes: a review. *Childs Nerv. Syst.,* **2008**, *24*(6), 685-692. [http://dx.doi.org/10.1007/s00381-008-0626-4] [PMID: 18373102]

[47] Graham, D.; Tisdall, M.M.; Gill, D. Corpus callosotomy outcomes in pediatric patients: A systematic review. *Epilepsia,* **2016**, *57*(7), 1053-1068. [http://dx.doi.org/10.1111/epi.13408] [PMID: 27237542]

[48] Morrell, F.; Whisler, W.W.; Bleck, T.P. Multiple subpial transection: a new approach to the surgical treatment of focal epilepsy. *J. Neurosurg.,* **1989**, *70*(2), 231-239. [http://dx.doi.org/10.3171/jns.1989.70.2.0231] [PMID: 2492335]

[49] Kawai, K. Epilepsy surgery: current status and ongoing challenges. *Neurol. Med. Chir. (Tokyo),* **2015**, *55*(5), 357-366. [http://dx.doi.org/10.2176/nmc.ra.2014-0414] [PMID: 25925752]

[50] Spencer, S.; Huh, L. Outcomes of epilepsy surgery in adults and children. *Lancet Neurol.,* **2008**, *7*(6), 525-537. [http://dx.doi.org/10.1016/S1474-4422(08)70109-1] [PMID: 18485316]

[51] Kaufmann, W.E.; Krauss, G.L.; Uematsu, S.; Lesser, R.P. Treatment of epilepsy with multiple subpial transections: an acute histologic analysis in human subjects. *Epilepsia,* **1996**, *37*(4), 342-352. [http://dx.doi.org/10.1111/j.1528-1157.1996.tb00570.x] [PMID: 8603639]

[52] Ntsambi-Eba, G.; Vaz, G.; Docquier, M.A.; van Rijckevorsel, K.; Raftopoulos, C. Patients with refractory epilepsy treated using a modified multiple subpial transection technique. *Neurosurgery,* **2013**, *72*(6), 890-897. [http://dx.doi.org/10.1227/NEU.0b013e31828ba750] [PMID: 23531857]

[53] Penry, J.K.; Dean, J.C. Prevention of intractable partial seizures by intermittent vagal stimulation in humans: preliminary results. *Epilepsia,* **1990**, *31*(Suppl. 2), S40-S43. [http://dx.doi.org/10.1111/j.1528-1157.1990.tb05848.x] [PMID: 2121469]

[54] Aalbers, M.W.; Rijkers, K.; Klinkenberg, S.; Majoie, M.; Cornips, E.M. Vagus nerve stimulation lead removal or replacement: surgical technique, institutional experience, and literature overview. *Acta Neurochir. (Wien),* **2015**, *157*(11), 1917-1924. [http://dx.doi.org/10.1007/s00701-015-2547-9] [PMID: 26335753]

[55] Schachter, S.C.; Saper, C.B. Vagus nerve stimulation. *Epilepsia,* **1998**, *39*(7), 677-686. [http://dx.doi.org/10.1111/j.1528-1157.1998.tb01151.x] [PMID: 9670894]

[56] Krahl, S.E.; Clark, K.B. Vagus nerve stimulation for epilepsy: A review of central mechanisms. *Surg. Neurol. Int.,* **2012**, *3*(Suppl. 4), S255-S259. [http://dx.doi.org/10.4103/2152-7806.103015] [PMID: 23230530]

[57] Panebianco, M.; Zavanone, C.; Dupont, S.; Restivo, D.A.; Pavone, A. Vagus nerve stimulation therapy in partial epilepsy: a review. *Acta Neurol. Belg.,* **2016**, *116*(3), 241-248. [http://dx.doi.org/10.1007/s13760-016-0616-3] [PMID: 26908034]

[58] Krahl, S.E.; Clark, K.B.; Smith, D.C.; Browning, R.A. Locus coeruleus lesions suppress the seizure-attenuating effects of vagus nerve stimulation. *Epilepsia,* **1998**, *39*(7), 709-714. [http://dx.doi.org/10.1111/j.1528-1157.1998.tb01155.x] [PMID: 9670898]

[59] Carpenter, L.L.; Moreno, F.A.; Kling, M.A.; Anderson, G.M.; Regenold, W.T.; Labiner, D.M.; Price, L.H. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biol. Psychiatry,* **2004**, *56*(6), 418-426. [http://dx.doi.org/10.1016/j.biopsych.2004.06.025] [PMID: 15364040]

[60] Pavlov, V.A.; Tracey, K.J. The vagus nerve and the inflammatory reflex--linking immunity and metabolism. *Nat. Rev. Endocrinol.,* **2012**, *8*(12), 743-754. [http://dx.doi.org/10.1038/nrendo.2012.189] [PMID: 23169440]

[61] Follesa, P.; Biggio, F.; Gorini, G.; Caria, S.; Talani, G.; Dazzi, L.; Puligheddu, M.; Marrosu, F.; Biggio, G. Vagus nerve stimulation increases norepinephrine concentration and the gene expression of BDNF and bFGF in the rat brain. *Brain Res.,* **2007**, *1179*, 28-34. [http://dx.doi.org/10.1016/j.brainres.2007.08.045] [PMID: 17920573]

[62] DeGiorgio, C.M.; Schachter, S.C.; Handforth, A.; Salinsky, M.; Thompson, J.; Uthman, B.; Reed, R.; Collins, S.; Tecoma, E.; Morris, G.L.; Vaughn, B.; Naritoku, D.K.; Henry, T.; Labar, D.; Gilmartin, R.; Labiner, D.; Osorio, I.; Ristanovic, R.; Jones, J.; Murphy, J.; Ney, G.; Wheless, J.; Lewis, P.; Heck, C. Prospective long-term study of vagus nerve stimulation for the treatment of refractory seizures. *Epilepsia,* **2000**, *41*(9), 1195-1200. [http://dx.doi.org/10.1111/j.1528-1157.2000.tb00325.x] [PMID: 10999559]

[63] Englot, D.J.; Chang, E.F.; Auguste, K.I. Vagus nerve stimulation for epilepsy: a meta-analysis of efficacy and predictors of response. *J. Neurosurg.,* **2011**, *115*(6), 1248-1255. [http://dx.doi.org/10.3171/2011.7.JNS11977] [PMID: 21838505]

[64] Pakdaman, H.; Amini, H.A.; Abbasi, M.; Karimi, M.; Arami, M.A.; Mosavi, S.A.; Haddadian, K.; Rezaei, O.; Sadeghi, S.; Sharifi, G.; Gharagozli, K.; Bahrami, P.; Ashrafi, F.; Kasmae, H.D.; Ghassemi, A.; Arabahmadi, M.; Behnam, B. Vagus nerve stimulation in drug-resistant epilepsy: the efficacy and adverse effects in a 5-year follow-up study in Iran. *Neurol. Sci.,* **2016**, *37*(11), 1773-1778. [http://dx.doi.org/10.1007/s10072-016-2661-3] [PMID: 27401807]

[65] Révész, D.; Rydenhag, B.; Ben-Menachem, E. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. *J. Neurosurg. Pediatr.,* **2016**, *18*(1), 97-104. [http://dx.doi.org/10.3171/2016.1.PEDS15534] [PMID: 27015521]

[66] Bauer, S.; Baier, H.; Baumgartner, C.; Bohlmann, K.; Fauser, S.; Graf, W.; Hillenbrand, B.; Hirsch, M.; Last, C.; Lerche, H.; Mayer, T.; Schulze-Bonhage, A.; Steinhoff, B.J.; Weber, Y.; Hartlep, A.; Rosenow, F.; Hamer, H.M. Transcutaneous vagus nerve stimulation (tVNS) for treatment of drug-resistant epilepsy: A randomized, double-blind clinical trial (cMPsE02). *Brain Stimul.,* **2016**, *9*(3), 356-363. [http://dx.doi.org/10.1016/j.brs.2015.11.003] [PMID: 27033012]

[67] Rong, P. Transcutaneous vagus nerve stimulation for refractory epilepsy: a randomized controlled trial. *Clin. Sci. (Lond),* **2014**. [Epub ahead of print]

[68] Fisher, R.; Salanova, V.; Witt, T.; Worth, R.; Henry, T.; Gross, R.; Oommen, K.; Osorio, I.; Nazzaro, J.; Labar, D.; Kaplitt, M.; Sperling, M.; Sandok, E.; Neal, J.; Handforth, A.; Stern, J.; DeSalles, A.; Chung, S.; Shetter, A.; Bergen, D.; Bakay, R.; Henderson, J.; French, J.; Baltuch, G.; Rosenfeld, W.; Youkilis, A.; Marks, W.; Garcia, P.; Barbaro, N.; Fountain, N.; Bazil, C.; Goodman, R.; McKhann, G.; Babu Krishnamurthy, K.; Papavassiliou, S.; Epstein, C.; Pollard, J.; Tonder, L.; Grebin, J.; Coffey, R.; Graves, N. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. *Epilepsia,* **2010**, *51*(5), 899-908. [http://dx.doi.org/10.1111/j.1528-1167.2010.02536.x] [PMID: 20331461]

[69] Ben-Menachem, E. Neurostimulation-past, present, and beyond. *Epilepsy Curr.,* **2012**, *12*(5), 188-191. [http://dx.doi.org/10.5698/1535-7511-12.5.188] [PMID: 23118604]

[70] Boviatsis, E.J.; Stavrinou, L.C.; Themistocleous, M.; Kouyialis, A.T.; Sakas, D.E. Surgical and hardware complications of deep brain stimulation. A seven-year experience and review of the literature. *Acta Neurochir. (Wien),* **2010**, *152*(12), 2053-2062. [http://dx.doi.org/10.1007/s00701-010-0749-8] [PMID: 20658301]

[71] Morrell, M.J. Responsive cortical stimulation for the treatment of medically intractable partial epilepsy. *Neurology,* **2011**, *77*(13), 1295-1304. [http://dx.doi.org/10.1212/WNL.0b013e3182302056] [PMID: 21917777]

[72] Fridley, J.; Thomas, J.G.; Navarro, J.C.; Yoshor, D. Brain stimulation for the treatment of epilepsy. *Neurosurg. Focus,* **2012**, *32*(3), E13. [http://dx.doi.org/10.3171/2012.1.FOCUS11334] [PMID: 22380854]

[73] Sohal, V.S.; Sun, F.T. Responsive neurostimulation suppresses synchronized cortical rhythms in patients with epilepsy. *Neurosurg. Clin. N. Am.,* **2011**, *22*(4), 481-488, vi. [vi.]. [http://dx.doi.org/10.1016/j.nec.2011.07.007] [PMID: 21939847]

[74] Cox, J.H.; Seri, S.; Cavanna, A.E. Clinical utility of implantable neurostimulation devices as adjunctive treatment of uncontrolled seizures. *Neuropsychiatr. Dis. Treat.,* **2014**, *10*, 2191-2200. [PMID: 25484587]

[75] Quigg, M.; Rolston, J.; Barbaro, N.M. Radiosurgery for epilepsy: clinical experience and potential antiepileptic mechanisms. *Epilepsia,* **2012**, *53*(1), 7-15. [http://dx.doi.org/10.1111/j.1528-1167.2011.03339.x] [PMID: 22191545]

[76] Chang, E.F.; Quigg, M.; Oh, M.C.; Dillon, W.P.; Ward, M.M.; Laxer, K.D.; Broshek, D.K.; Barbaro, N.M. Predictors of efficacy after stereotactic radiosurgery for medial temporal lobe epilepsy. *Neurology,* **2010**, *74*(2), 165-172. [http://dx.doi.org/10.1212/WNL.0b013e3181c9185d] [PMID: 20065252]

[77] Przybylowski, C.J.; Ding, D.; Starke, R.M.; Yen, C.P.; Quigg, M.; Dodson, B.; Ball, B.Z.; Sheehan, J.P. Seizure and anticonvulsant outcomes following stereotactic radiosurgery for intracranial arteriovenous malformations. *J. Neurosurg.,* **2015**, *122*(6), 1299-1305. [http://dx.doi.org/10.3171/2014.11.JNS141388] [PMID: 25614948]

[78] Hawasli, A.H.; Bandt, S.K.; Hogan, R.E.; Werner, N.; Leuthardt, E.C. Laser ablation as treatment strategy for medically refractory dominant insular epilepsy: therapeutic and functional considerations. *Stereotact. Funct. Neurosurg.,* **2014**, *92*(6), 397-404. [http://dx.doi.org/10.1159/000366001] [PMID: 25359500]

[79] Englot, D.J.; Birk, H.; Chang, E.F. Seizure outcomes in nonresective epilepsy surgery: an update. *Neurosurg. Rev.,* **2016**. [PMID: 27206422]

[80] Lewis, E.C.; Weil, A.G.; Duchowny, M.; Bhatia, S.; Ragheb, J.; Miller, I. MR-guided laser interstitial thermal therapy for pediatric drug-resistant lesional epilepsy. *Epilepsia,* **2015**, *56*(10), 1590-1598. [http://dx.doi.org/10.1111/epi.13106] [PMID: 26249524]

[81] Kang, J.Y.; Wu, C.; Tracy, J.; Lorenzo, M.; Evans, J.; Nei, M.; Skidmore, C.; Mintzer, S.; Sharan, A.D.; Sperling, M.R. Laser interstitial thermal therapy for medically intractable mesial temporal lobe epilepsy. *Epilepsia,* **2016**, *57*(2), 325-334. [http://dx.doi.org/10.1111/epi.13284] [PMID: 26697969]

[82] Chugani, H.T. Surgical treatment for refractory epileptic spasms: The Detroit se-ries. **2015**, *56*(12), 1941-49.

[83] Althausen, A.; Gleissner, U.; Hoppe, C.; Sassen, R.; Buddewig, S.; von Lehe, M.; Schramm, J.; Elger, C.E.; Helmstaedter, C. Long-term outcome of hemispheric surgery at different ages in 61 epilepsy patients. *J. Neurol. Neurosurg. Psychiatry,* **2013**, *84*(5), 529-536. [http://dx.doi.org/10.1136/jnnp-2012-303811] [PMID: 23268362]

[84] Cole, A.J.; Wiebe, S. Debate: Should antiepileptic drugs be stopped after successful epilepsy surgery? *Epilepsia,* **2008**, *49*(Suppl. 9), 29-34. [http://dx.doi.org/10.1111/j.1528-1167.2008.01924.x] [PMID: 19087115]

[85] Lukyanetz, E.A.; Shkryl, V.M.; Kostyuk, P.G. Selective blockade of N-type calcium channels by levetiracetam. *Epilepsia,* **2002**, *43*(1), 9-18. [http://dx.doi.org/10.1046/j.1528-1157.2002.24501.x] [PMID: 11879381]

[86] Rigo, J.M.; Hans, G.; Nguyen, L.; Rocher, V.; Belachew, S.; Malgrange, B.; Leprince, P.; Moonen, G.; Selak, I.; Matagne, A.; Klitgaard, H. The anti-epileptic drug levetiracetam reverses the inhibition by negative allosteric modulators of neuronal GABA- and glycine-gated currents. *Br. J. Pharmacol.,* **2002**, *136*(5), 659-672. [http://dx.doi.org/10.1038/sj.bjp.0704766] [PMID: 12086975]

[87] Jehi, L.E.; Irwin, A.I.; Kayyali, H.; Vadera, S.; Bingaman, W.; Najm, I. Levetiracetam may favorably affect seizure outcome after temporal lobectomy. *Epilepsia,* **2012**, *53*(6), 979-986. [http://dx.doi.org/10.1111/j.1528-1167.2012.03453.x] [PMID: 22462729]

[88] Menon, R.; Rathore, C.; Sarma, S.P.; Radhakrishnan, K. Feasibility of antiepileptic drug withdrawal following extratemporal resective epilepsy surgery. *Neurology,* **2012**, *79*(8), 770-776. [http://dx.doi.org/10.1212/WNL.0b013e3182644f7d] [PMID: 22843256]

[89] Park, K.I.; Lee, S.K.; Chu, K.; Jung, K.H.; Bae, E.K.; Kim, J.S.; Lee, J.J.; Lee, S.Y.; Chung, C.K. Withdrawal of antiepileptic drugs after neocortical epilepsy surgery. *Ann. Neurol.,* **2010**, *67*(2), 230-238. [http://dx.doi.org/10.1002/ana.21884] [PMID: 20225284]

[90] Bancaud, J.; Angelergues, R.; Bernouilli, C.; Bonis, A.; Bordas-Ferrer, M.; Bresson, M.; Buser, P.; Covello, L.; Morel, P.; Szikla, G.; Takeda, A.; Talairach, J. Functional stereotaxic exploration (SEEG) of epilepsy. *Electroencephalogr. Clin. Neurophysiol.,* **1970**, *28*(1), 85-86. [PMID: 4188481]

[91] Duncan, J.S. Imaging in the surgical treatment of epilepsy. *Nat. Rev. Neurol.,* **2010**, *6*(10), 537-550. [http://dx.doi.org/10.1038/nrneurol.2010.131] [PMID: 20842185]

[92] Bien, C.G.; Szinay, M.; Wagner, J.; Clusmann, H.; Becker, A.J.; Urbach, H. Characteristics and surgical outcomes of patients with refractory magnetic resonance imaging-negative epilepsies. *Arch. Neurol.,* **2009**, *66*(12), 1491-1499. [http://dx.doi.org/10.1001/archneurol.2009.283] [PMID: 20008653]

[93] Bonelli, S.B.; Thompson, P.J.; Yogarajah, M.; Vollmar, C.; Powell, R.H.; Symms, M.R.; McEvoy, A.W.; Micallef, C.; Koepp, M.J.; Duncan, J.S. Imaging language networks before and after anterior temporal lobe resection: results of a longitudinal fMRI study. *Epilepsia,* **2012**, *53*(4), 639-650. [http://dx.doi.org/10.1111/j.1528-1167.2012.03433.x] [PMID: 22429073]

[94] Englot, D.J.; Nagarajan, S.S.; Imber, B.S.; Raygor, K.P.; Honma, S.M.; Mizuiri, D.; Mantle, M.; Knowlton, R.C.; Kirsch, H.E.; Chang, E.F. Epileptogenic zone localization using magnetoencephalography predicts seizure freedom in epilepsy surgery. *Epilepsia,* **2015**, *56*(6), 949-958. [http://dx.doi.org/10.1111/epi.13002] [PMID: 25921215]

[95] Van Paesschen, W.; Dupont, P.; Van Driel, G.; Van Billoen, H.; Maes, A. SPECT perfusion changes during complex partial seizures in patients with hippocampal sclerosis. *Brain,* **2003**, *126*(Pt 5), 1103-1111. [http://dx.doi.org/10.1093/brain/awg108] [PMID: 12690050]

[96] Goodfellow, M.; Rummel, C.; Abela, E.; Richardson, M.P.; Schindler, K.; Terry, J.R. Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. *Sci. Rep.,* **2016**, *6*, 29215. [http://dx.doi.org/10.1038/srep29215] [PMID: 27384316]

[97] Grouiller, F.; Thornton, R.C.; Groening, K.; Spinelli, L.; Duncan, J.S.; Schaller, K.; Siniatchkin, M.; Lemieux, L.; Seeck, M.; Michel, C.M.; Vulliemoz, S. With or without spikes: Localization of focal epileptic activity by simultaneous electroencephalography and functional magnetic resonance imaging. *Brain,* **2011**, *134*(Pt 10), 2867-2886. [http://dx.doi.org/10.1093/brain/awr156] [PMID: 21752790]

[98] Ryvlin, P.; Cross, J.H.; Rheims, S. Epilepsy surgery in children and adults. *Lancet Neurol.,* **2014**, *13*(11), 1114-1126. [http://dx.doi.org/10.1016/S1474-4422(14)70156-5] [PMID: 25316018]

[99] Lasoń, W.; Chlebicka, M.; Rejdak, K. Research advances in basic mechanisms of seizures and antiepileptic drug action. *Pharmacol. Rep.,* **2013**, *65*(4), 787-801. [http://dx.doi.org/10.1016/S1734-1140(13)71060-0] [PMID: 24145073]

[100] Kohl, M.M.; Paulsen, O. The roles of GABAB receptors in cortical network activity. *Adv. Pharmacol.,* **2010**, *58*, 205-229. [http://dx.doi.org/10.1016/S1054-3589(10)58009-8] [PMID: 20655484]

[101] Rajakulendran, S.; Hanna, M.G. The role of calcium channels in epilepsy. *Cold Spring Harb. Perspect. Med.,* **2016**, *6*(1), a022723. [http://dx.doi.org/10.1101/cshperspect.a022723] [PMID: 26729757]

[102] Nazıroğlu, M. TRPV1 channel: A potential drug target for treating epilepsy. *Curr. Neuropharmacol.,* **2015**, *13*(2), 239-247. [http://dx.doi.org/10.2174/1570159X13666150216222543] [PMID: 26411767]

[103] Manna, S.S.; Umathe, S.N. A possible participation of transient receptor potential vanilloid type 1 channels in the antidepressant effect of fluoxetine. *Eur. J. Pharmacol.,* **2012**, *685*(1-3), 81-90. [http://dx.doi.org/10.1016/j.ejphar.2012.04.023] [PMID: 22542657]

[104] Haas, M.; Forbush, B., III. The Na-K-Cl cotransporter of secretory epithelia. *Annu. Rev. Physiol.,* **2000**, *62*, 515-534. [http://dx.doi.org/10.1146/annurev.physiol.62.1.515] [PMID: 10845101]

[105] Jaggi, A.S.; Kaur, A.; Bali, A.; Singh, N. Expanding spectrum of sodium potassium chloride Co-transporters in the pathophysiology of diseases. *Curr. Neuropharmacol.,* **2015**, *13*(3), 369-388. [http://dx.doi.org/10.2174/1570159X13666150205130359] [PMID: 26411965]

[106] Sen, A.; Martinian, L.; Nikolic, M.; Walker, M.C.; Thom, M.; Sisodiya, S.M. Increased NKCC1 expression in refractory human epilepsy. *Epilepsy Res.,* **2007**, *74*(2-3), 220-227. [http://dx.doi.org/10.1016/j.eplepsyres.2007.01.004] [PMID: 17344024]

[107] Mylvaganam, S.; Ramani, M.; Krawczyk, M.; Carlen, P.L. Roles of gap junctions, connexins, and pannexins in epilepsy. *Front. Physiol.,* **2014**, *5*, 172. [http://dx.doi.org/10.3389/fphys.2014.00172] [PMID: 24847276]

[108] Manjarrez-Marmolejo, J.; Franco-Pérez, J. Gap junction blockers: An overview of their effects on induced seizures in animal models. *Curr. Neuropharmacol.,* **2016**, *14*(7), 759-771. [http://dx.doi.org/10.2174/1570159X14666160603115942] [PMID: 27262601]

[109] Rumià, J.; Marmol, F.; Sanchez, J.; Giménez-Crouseilles, J.; Carreño, M.; Bargalló, N.; Boget, T.; Pintor, L.; Setoain, X.; Donaire, A.; Saez, G.T.; Ribalta, T.; Ferrer, E.; Puig-Parellada, P. Oxidative stress markers in the neocortex of drug-resistant epilepsy patients submitted to epilepsy surgery. *Epilepsy Res.,* **2013**, *107*(1-2), 75-81. [http://dx.doi.org/10.1016/j.eplepsyres.2013.08.020] [PMID: 24054426]

[110] Dominiak, A.; Wilkaniec, A.; Wroczyński, P.; Adamczyk, A. Selenium in the therapy of neurological diseases. Where is it going? *Curr. Neuropharmacol.,* **2016**, *14*(3), 282-299. [http://dx.doi.org/10.2174/1570159X14666151223100011] [PMID: 26549649]

[111] Qian, F.; Tang, F.R. Metabotropic glutamate receptors and interacting proteins in epileptogenesis. *Curr. Neuropharmacol.,* **2016**, *14*(5), 551-562. [http://dx.doi.org/10.2174/1570159X14666160331142228] [PMID: 27030135]

[112] Wilder, R.M. The effect of ketonemia on the course of epilepsy. *Mayo Clin. Bulletin,* **1921**, *2*, 307-308.

[113] Kossoff, E.H.; Zupec-Kania, B.A.; Amark, P.E.; Ballaban-Gil, K.R.; Christina, B.A.G.; Blackford, R.; Buchhalter, J.R.; Caraballo, R.H.; Helen, C.J.; Dahlin, M.G.; Donner, E.J.; Klepper, J.; Jehle, R.S.; Kim, H.D.; Christiana Liu, Y.M.; Nation, J.; Nordli, D.R., Jr; Pfeifer, H.H.; Rho, J.M.; Stafstrom, C.E.; Thiele, E.A.; Turner, Z.; Wirrell, E.C.; Wheless, J.W.; Veggiotti, P.; Vining, E.P. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia,* **2009**, *50*(2), 304-317. [http://dx.doi.org/10.1111/j.1528-1167.2008.01765.x] [PMID: 18823325]

[114] Lambrechts, D.A. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. *Acta Neurol. Scand.,* **2017**, *135*(6), 678. [PMID: 27027847]

[115] Xiao, F. Review of the use of botanicals for epilepsy in complementary medical systems--traditional chinese medicine. *Epilepsy Behav,* **2015**, *52*(Pt B), 281-289.

[116] Schachter, S.C. Botanicals and herbs: a traditional approach to treating epilepsy. *Neurotherapeutics,* **2009**, *6*(2), 415-420. [http://dx.doi.org/10.1016/j.nurt.2008.12.004] [PMID: 19332338]

[117] Hung-Ming, W.; Liu, C.S.; Tsai, J.J.; Ko, L.Y.; Wei, Y.H. Antioxidant and anticonvulsant effect of a modified formula of chaihu-longu-muli-tang. *Am. J. Chin. Med.,* **2002**, *30*(2-3), 339-346. [PMID: 12230022]

[118] He, L.; Wen, T.; Yan, S.; Li, R.; Liu, Z.; Ren, H.; Liu, J.; Zhang, F.; Wu, J.; Liu, J. Reevaluation of the effect of Dianxianning on seizure rate of refractory epilepsy as additive treatment in clinical practice. *Front. Med.,* **2011**, *5*(2), 229-234. [http://dx.doi.org/10.1007/s11684-011-0139-5] [PMID: 21695630]

[119] Melvin, J.J.; Huntley, H.H. Immunomodulatory treatments in epilepsy. *Semin. Pediatr. Neurol.,* **2014**, *21*(3), 232-237. [http://dx.doi.org/10.1016/j.spen.2014.08.001] [PMID: 25510946]

[120] Wykes, R.C.; Heeroma, J.H.; Mantoan, L.; Zheng, K.; MacDonald, D.C.; Deisseroth, K.; Hashemi, K.S.; Walker, M.C.; Schorge, S.; Kullmann, D.M. Optogenetic and potassium channel gene therapy in a rodent model of focal neocortical epilepsy. *Sci. Transl. Med.,* **2012**, *4*(161), 161ra152. [http://dx.doi.org/10.1126/scitranslmed.3004190] [PMID: 23147003]

[121] Ledri, L.N.; Melin, E.; Christiansen, S.H.; Gøtzsche, C.R.; Cifra, A.; Woldbye, D.P.; Kokaia, M. Translational approach for gene therapy in epilepsy: Model system and unilateral overexpression of

neuropeptide Y and Y2 receptors. *Neurobiol. Dis.,* **2016**, *86*, 52-61. [http://dx.doi.org/10.1016/j.nbd.2015.11.014] [PMID: 26607785]

[122] Noè, F.; Pool, A.H.; Nissinen, J.; Gobbi, M.; Bland, R.; Rizzi, M.; Balducci, C.; Ferraguti, F.; Sperk, G.; During, M.J.; Pitkänen, A.; Vezzani, A. Neuropeptide Y gene therapy decreases chronic spontaneous seizures in a rat model of temporal lobe epilepsy. *Brain,* **2008**, *131*(Pt 6), 1506-1515. [http://dx.doi.org/10.1093/brain/awn079] [PMID: 18477594]

[123] Richichi, C.; Lin, E.J.; Stefanin, D.; Colella, D.; Ravizza, T.; Grignaschi, G.; Veglianese, P.; Sperk, G.; During, M.J.; Vezzani, A. Anticonvulsant and antiepileptogenic effects mediated by adeno-associated virus vector neuropeptide Y expression in the rat hippocampus. *J. Neurosci.,* **2004**, *24*(12), 3051-3059. [http://dx.doi.org/10.1523/JNEUROSCI.4056-03.2004] [PMID: 15044544]

[124] Noe, F.; Vaghi, V.; Balducci, C.; Fitzsimons, H.; Bland, R.; Zardoni, D.; Sperk, G.; Carli, M.; During, M.J.; Vezzani, A. Anticonvulsant effects and behavioural outcomes of rAAV serotype 1 vector-mediated neuropeptide Y overexpression in rat hippocampus. *Gene Ther.,* **2010**, *17*(5), 643-652. [http://dx.doi.org/10.1038/gt.2010.23] [PMID: 20220782]