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Innovative methods of treating drug-resistant epilepsy: Review of the latest reports

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Abstract

Information and purpose: Drug-resistant epilepsy (DRE) affects about one-third of epilepsy patients, posing a serious challenge despite numerous available antiepileptic drugs. For patients who do not respond to pharmacological treatment, alternative approaches are needed. This study aims to present selected non-pharmacological methods for treating DRE.

Material and methods: The review is based on publicly available sources, focusing on articles published between 2020 and 2025 in the PubMed database. Historical context was drawn from literature dating back to the 1990s.
Results: Common non-pharmacological treatments include surgery, neurostimulation, and the ketogenic diet. These methods have proven effective in reducing seizure frequency and improving quality of life. They offer personalized and well-tolerated options suitable for different age groups.
Conclusions: Non-pharmacological treatments for DRE are valuable alternatives for patients not benefiting from medication. Their efficacy and safety support their growing use in modern clinical practice.
Keywords: drug-resistant epilepsy, treatment of epilepsy, brain stimulation, epilepsy surgery, ketogenic diet

Introduction

Epilepsy is a chronic neurological disorder involving repeated seizures or other brain dysfunction. It is caused by abnormal neuronal discharges. [1] The criteria for diagnosis include the occurrence of at least two epileptic seizures not more than 24 hours apart or one unprovoked seizure when there is a high risk of another seizure (about 60%) or a diagnosis of status epilepticus. [2] The condition affects about 70 million people worldwide. [3]

A large proportion of patients are seizure free through the use of antiepileptic drugs, while 1/3 develop drug resistant epilepsy. [4] The variable pathophysiology and clinical response to therapy make it a difficult condition to control in modern medicine. Epilepsy can be declared drug-resistant when remission is not achieved despite the use of two appropriately selected, tolerated and administered in the correct doses of antiepileptic drugs. It results in reduced quality of life, increased risk of injury, emotional problems including depression or increased mortality. [5] In such cases, non-pharmacological methods are of great importance. They make it possible to reduce the number of seizures, improve quality of life and sometimes make it possible to reduce the dose of medications and therefore their unwanted effects. They can be used alone or as an adjunct to pharmacotherapy.

The review is based on the latest articles from the PubMed database in the years 2020-2025. Keywords like drug-resistant epilepsy, treatment of epilepsy, brain stimulation, epilepsy surgery, ketogenic diet were used in the investigation.

Materials and methods

All data collected from publicly available sources. The review was based on research of articles published from 2020 to 2025 on the PubMed database using the following keywords: drug-resistant epilepsy, treatment of epilepsy, brain stimulation, epilepsy surgery, ketogenic diet. A historical overview based on articles from the 1990s was also included.

Objective

The objective of this study is to present and analyze modern, non-pharmacological methods of treating drug-resistant epilepsy. These include epilepsy surgery, neurostimulation, and the ketogenic diet. The article evaluates the effectiveness, indications, and limitations of these therapies, and emphasizes the importance of their proper selection in the context of an individualized approach to a patient with drug-resistant epilepsy.

DESCRIPTION OF STATE OF KNOWLEDGE

Surgery

The history of epilepsy surgery dates back to ancient times. At that time, it included such procedures as cranial trepanation to relieve seizures. It has evolved considerably over the years. The modern era of epilepsy surgery was started in the 20th century with the development of electroencephalography (EEG). It made it possible to precisely localize epileptic focal points. This provided the opportunity to develop targeted surgical procedures during which areas causing seizures were removed. It originally concentrated on procedures such as temporal lobectomy. Surgical outcomes were improved by the development of neuroimaging including magnetic resonance imaging. This made it possible to accurately plan procedures. Today, modern minimally invasive techniques such as LITT, RNS, MRgFUS are also available. They are effective with less risk to the patient and shorter recovery time [6].

An important development in surgery is SEE-an advanced diagnostic technique that allows three-dimensional mapping of epileptiform activity in deep brain structures. It is used in patients with difficult-to-localize seizures, especially in cases where MRI does not show changes. Through careful planning and insertion of electrodes through small holes in the skull, SEEG allows identification of the exact source and propagation pathways of seizures, assessment of complex epileptic networks, and protection of functional brain areas (such as speech or movement).

SEEG not only supports surgical decisions, but also enables integration with therapies such as RNS, LITT or coagulation, providing personalized, precise treatment for drug-resistant epilepsy [7].

Subdural electrodes

Subdural electrodes are a key element in the invasive diagnosis of epilepsy. They are used especially when non-invasive methods fail to localize seizure foci. After a craniotomy is performed, they are placed on the cerebral cortex. In this way, they mediate the recording of electrical activity with high precision [8].

This technique allows accurate localization of epileptic zones, detailed functional mapping of the cerebral cortex (e.g., speech or motor centers), and planning for resection while preserving key neurological functions,

Long-term monitoring of seizure and interictal activity allows the collection of comprehensive data to support surgical decisions. Although they require craniotomy and carry a risk of complications (infection, hemorrhage, edema), advances in electrode design and surgical techniques have increased their safety [6].

Robot-assisted surgery

Robot-assisted surgery represents a breakthrough in the diagnosis and treatment of epilepsy, especially in procedures such as SEEG and subdural electrode implantation. Robotic systems enable extremely precise planning and guidance of stereo electroencephalography, minimizing the risk of complications and human error. Robots increase patient safety, shorten recovery time, reduce postoperative pain and the risk of infection and length of hospitalization.

Robotics is also finding applications in medical treatment, including during percutaneous thermotherapy (LITT) and resection of epileptic foci. In the future, robotic surgery is expected to advance through the integration of artificial intelligence, augmented reality and real-time intraoperative imaging, paving the way for even more personalized and effective treatment of drug-resistant epilepsy [10][9].

Ablation in the treatment of epilepsy

Ablation procedures are an important area of modern epilepsy surgery. They offer precise and minimally invasive treatments for drug-resistant epilepsy. Prominent among the advanced techniques are:

- Radiofrequency thermocoagulation (RF-TC), which uses radio waves to create controlled ablation foci in the brain, interrupting seizure circuits without the need for open surgery.

- Laser interstitial therapy under magnetic resonance imaging (LITT), which allows precise removal of epileptic foci with minimal damage to surrounding tissues.
- Magnetic resonance-guided focused ultrasound (MRgFUS), which allows non-invasive destruction of seizure sources through focused tissue heating.

Each provides a modern, targeted approach to treating difficult cases of epilepsy, combining high efficacy with limited surgical risk.

A 2020 meta-analysis analyzed a total of 551 patients. It showed that 58% of patients with temporal lobe epilepsy achieved seizure freedom after LITT [10].

A study published in 2020 in the journal Epilepsy & Behavior, analyzed the outcomes of 234 patients with mTLE undergoing LITT. After 12 months of follow-up, 58% of patients achieved complete seizure freedom (Engel class I), and 74% had a significant reduction in seizures (Engel classes I-II). In addition, shorter hospitalization times and lower risk of complications were reported compared to traditional temporal lobectomy [11].

LITT is a promising alternative to traditional surgery in the treatment of drug-resistant epilepsy, offering efficacy comparable to more invasive methods while reducing risk and recovery time. It is particularly beneficial for patients who are ineligible for conventional surgery or who prefer a less invasive approach.

A systematic review of 20 studies involving 360 patients showed that RF-TC is an effective treatment for drug-resistant epilepsy. After 12 months of follow-up, 62% of patients achieved a favorable treatment outcome. Factors contributing to better outcomes included the presence of MRI lesions, the use of monopolar RF-TC and a higher number of ablations performed. The percentage of permanent neurological complications was 2%

An analysis of 93 pediatric cases showed that RF-TC is an effective and safe treatment for epilepsy in children. In studies involving only children, 90% of patients were responders, and 71% achieved seizure freedom after one year. In the pooled analysis, seizure freedom was achieved in 45.2% of patients, and the percentage of responders was 74.2%. Low rates of complications, mainly transient neurological deficits, were reported [12].

RF-TC is a minimally invasive and effective treatment for drug-resistant epilepsy, both in adults and children. Particularly favorable results are observed in patients with visible MRI lesions and in cases of medial temporal lobe epilepsy. RF-TC may also be considered as an alternative to more invasive surgical procedures

A 2022 pilot study evaluated the effects of low-intensity focused ultrasound on patients with drug-resistant epilepsy. A reduction in seizure frequency was observed in 33% of participants, and some showed improvement in EEG recordings. Side effects were mild and included transient neurological symptoms. The results indicate the potential of MRgFUS as a non-invasive method of neuromodulation in the treatment of epilepsy

VNS vagus nerve stimulation

The vagus nerve (X) is the longest mixed cranial nerve. It belongs to the autonomic nervous system. It extends bilaterally from the brainstem to the abdominal cavity innervating the thoracic and abdominal organs.[13]

Vagus nerve stimulation was first studied in 1938 when Bailey and Bremmer observed electrographic changes in cats that resulted from X nerve stimulation. The breakthrough came in 1985 when Zabara and colleagues showed that vagus nerve stimulation could effectively interrupt epileptic seizures in dogs. These discoveries formed the basis for the first use of VNS in humans, conducted by Penry in 1988 [14] [15]. The anticonvulsant mechanisms of VNS are not fully understood. However, there is evidence that norepinephrine plays a major role in the process. The vagus nerve passes through the sinusoidal site - the main noradrenergic nucleus in the brain. When the sinus place was ablated in rodents, the VNS lost its antiepileptic effect [16].

The modern invasive VNS device consists of 3 components: 1.A pulse generator placed subcutaneously in the thoracic region, 2.An electrode cuff wrapped around the left cervical vagus nerve, and 3.A cable connecting the generator to the electrode. Once the device is implanted, the pacing parameters are individually programmed to maximize treatment efficacy and minimize side effects [16].

A multicenter, randomized, double-blind study evaluated the efficacy of vagus nerve stimulation (VNS) in 114 patients with refractory partial seizures of epilepsy. After implantation of the stimulators, patients were randomly assigned to a group with high (therapeutic) or low (ineffective) VNS parameters for 14 weeks. Response to treatment was defined as a reduction in seizures of at least 50%. At the end of the study, a total of 31% of participants were responding to treatment. The group with high VNS had a significantly greater reduction in seizure frequency (25% on average) compared to the group with low VNS (6%). The therapy was well tolerated.High VNS is an effective and safe adjunctive treatment for drug-resistant epilepsy with partial seizures [17].

Another study by Handforth and colleagues also compared high and low vagus nerve stimulation (VNS) in patients with drug-resistant partial seizures. Patients in the treatment group experienced an average 28% reduction in seizures, compared to 15% in the control group.

There was also a better assessment of overall health in patients with high stimulation. Side effects included a change in voice and shortness of breath, but there were no negative effects on vital functions. [18]

Scherman and colleagues obtained a response rate of 45%. In addition, they found that a standard duty cycle (stimulation period of 30s) had better results than a rapid cycle (stimulation period of 7s). [19]

Based on these data, contemporary studies have confirmed the efficacy of this method as a therapeutic option. In 2021, a meta-analysis written by Jaina observed the results of VNS in pediatric patients from 99 articles and 3474 patients. The authors presented that 56.4% of patients experienced a reduction in seizures of more than 50% [20]. In another study, participants were divided into two groups: one underwent transcutaneous vagus nerve stimulation (ta-VNS) and the other simulated (placebo). The intervention lasted several weeks, and seizure frequency, quality of life and possible side effects were assessed. In 44.74% of patients undergoing active stimulation, there was a ≥50% reduction in seizures. In addition, patients using ta-VNS showed a significant improvement in quality of life, as well as a reduction in anxiety and depression. The incidence of side effects was low and comparable between groups - mainly mild local symptoms, such as tingling or redness of the skin [21]

Vagus nerve stimulation is an effective, safe and long-term beneficial adjunctive treatment for refractory epilepsy in both children and adults. Although complete resolution of seizures is rare, a significant proportion of patients experience a significant improvement in quality of life. The therapy is generally well tolerated, and side effects - such as voice change, hoarseness, shortness of breath, coughing or throat discomfort - are usually mild in nature and often resolve over time or after adjusting stimulation parameters.

Deep brain stimulation DBS

Deep brain stimulation is a modern method of neurological treatment in which electrical impulses are sent to selected deep brain structures. The technique was first used in the 1990s to treat movement disorders such as Parkinson's disease, dystonia and spontaneous tremor. Over time, it has also gained acceptance in cases of drug-resistant epilepsy. [22] [23].

The procedure involves implanting electrodes in a specific area of the brain, which are then connected by wires to a pulse generator placed subcutaneously in the chest. The entire system is computer-controlled, allowing the stimulation parameters to be individually adjusted to the patient's needs. An important advantage of DBS is the adjustability and reversibility of the procedure, which distinguishes it from classical surgical methods [24].

Although several targets have been found to be affected by DBS, the most scientific data has been reported in relation to stimulation of the anterior thalamic nucleus (ANT) [18]. It has a significant role in limbic and temporal lobe epilepsies [25]. The first attempts to use DBS in the treatment of epilepsy took place in the 1980s by Irvin Cooper. Based on these studies, pilot studies using ANT stimulation in patients with temporal lobe epileptic seizures were initiated.

The SANTE study, which tested stimulation of the anterior thalamic nucleus in the treatment of drug-resistant epilepsy, proved to be pivotal. It was observed that after one year of deep brain stimulation (DBS), the median seizure reduction was 41%, and after five years, 69%. The percentage of patients with ≥50% seizure reduction increased from 43% after one year to 68% after five years. Sixteen percent of patients experienced at least six months of seizure remission [26]. Further observations published in 2021 showed sustained benefit after 10 years with a 75% reduction in median seizures and improved quality of life. Additionally, it was found that DBS can reduce the risk of sudden unexpected death in epilepsy (SUDEP) [27].

Another study- based on the MORE multicenter registry- evaluated the efficacy of ANT-DBS in 170 patients. After 2 years, the median monthly number of seizures decreased by 33.1%, and the response rate (≥50% reduction) was 32.3%. In 47 patients followed up for 5 years, the seizure frequency reduction reached 55.1%, and the response rate was 53.2%. Better results were obtained in centers with more experience (more than 10 implantations) [28].

The effectiveness of DBS is also confirmed by meta-analyses. Elshymaa E Raslan and colleagues, based on 29 articles retrieved for screening and 5 randomized control trials, showed a significant improvement in seizure control. The effect size for seizure frequency reduction was 0.51, and for response rate was 0.54 [29].

A recent systematic review of deep brain stimulation in children with DRE demonstrated the effectiveness of thalamic DBS in pediatric populations as well. The analysis of 52 cases showed that a reduction in seizure frequency of more than 50% was achieved in 9 of 14 children after anterior thalamic nucleus stimulation (ANT-DBS) and in 31 of 38 children after medial thalamic nucleus stimulation (CM-DBS). The procedure was well tolerated, and the most common complication - occurring in 10% of patients - was infection [30].

DBS is an effective and safe treatment for drug-resistant epilepsy, especially in patients who are ineligible for surgical treatment. Long-term clinical data (SANTE, MORE) confirm the durability of therapeutic effects and improvement in quality of life. The pediatric population also benefits from deep brain stimulation. However, further research is needed, especially to understand the mechanisms of action of DBS.

Responsive Neurostimulation (RNS)

Responsive Neurostimulation (RNS) is a method developed to address the patient individually. It works on a “closed loop” principle - the device constantly monitors the brain's electrical activity and detects the potential onset of an epileptic seizure. When it detects abnormal activity, it immediately sends precisely targeted electrical stimulation to interrupt or attenuate the activity before a full-blown seizure occurs.[31][32] The system consists of a neurostimulator implant and electrodes placed in the area of the brain that is responsible for initiating a seizure[33]. The first device was approved in 2013 by the Food and Drug Administration (FDA)[32].

Dorian M. Kusyk et al. presented a systematic review and meta-analysis that ultimately included 541 patients. They showed that the average response rate (patients with >50% reduction in seizures) was 68%[34].

This data was confirmed by a study published in 2025 in China. It analyzed efficacy in subjects treated with RNS for drug-resistant focal epilepsy. The follow-up period for the 19 participants was 10.7± 3.4 months. They found that the number of seizures decreased significantly as early as 6 months after starting the device with a median reduction in seizure frequency of 48% at month 6 and 58% at month 12. No serious adverse effects were reported [35].

Regarding the pediatric population, Adam S.Levy et al. published a meta-analysis that included children with an average age of 14 years. Of these patients, 42% had previous resection surgery and 18% had vagus nerve stimulation. After one year of follow-up, the median reduction in epileptic seizures reached 75%. The complication rate oscillated at 8.4%, with half being infectious complications [36]. The safety of RNS in children is also confirmed by the results of a retrospective study by Fyodor Panov et al. Of 27 patients, three developed complications in the form of infection. They were treated with antibiotics. Among them, one required partial removal of the system and one required complete removal. No other complications were observed [37].

Responsive neurostimulation (RNS) is an effective and relatively safe adjunct therapy for drug-resistant epilepsy - both in adults and children. Results in the pediatric population are particularly promising, although further well-designed studies with a larger group of patients are needed. Better selection of candidates for RNS could significantly improve future treatment options for DRE from a young age.

Ketogenic diet

The ketogenic diet (KD) is a specialized diet characterized by very low carbohydrates, high fats and moderate or tailored amounts of protein [38]. The main goal of this diet is to put the body into a state of ketosis - a metabolic state resembling fasting, in which the body switches from using glucose as its primary energy source to burning fats. The product of this process is ketone bodies produced in the liver, which can serve as alternative fuel, especially for the brain [39].

The history of ketogenic diet therapy dates back to ancient times - already Hippocrates used dietary restrictions to treat epileptic seizures. In the 19th century, a case was reported of a boy whose seizures ceased as a result of fasting treatment administered by a healer. As knowledge of metabolism developed, fasting was replaced by a high-fat diet designed to mimic the effects of starvation. However, the introduction of phenytoin in 1938, followed by the development of more antiepileptic drugs, led to a significant reduction in the use of the ketogenic diet. Its popularity was revived in 1994, when the therapy was used with complete success in a two-year-old boy with drug-resistant epilepsy at Johns Hopkins Hospital - the child achieved a seizure-free state, and his psychophysical development improved markedly.

The exact mechanisms of the anticonvulsant effect of the ketogenic diet are not yet fully understood. One of the main factors considered important for its effectiveness is the elevation of the level of ketone bodies in the blood. It is believed that ketones have anticonvulsant properties - they serve as an alternative source of energy for the brain, supporting neuronal function and stabilizing neuronal excitability, which may reduce the risk of seizures[39].

In addition, the ketogenic diet may affect the balance of neurotransmitters in the central nervous system. By promoting a reduction in excitatory neurotransmitters and increasing inhibitory neurotransmitters, it may contribute to suppressing seizure activity and improving seizure control[39].

The modified Atkins diet (MAD) is a less restrictive and better tolerated alternative to the classical ketogenic diet (KD). It retains a similar mechanism of action, especially in the treatment of drug-resistant epilepsy (DRE). Unlike traditional KD, MAD does not require a fasting period or restrictions on caloric or fluid intake. Protein and fat can be consumed without restriction.

The diet is based on a fat-to-carbohydrate ratio of about 1:1 and does not impose strict rules on meal planning. The daily carbohydrate limit is usually around 25 grams, which allows the patient to maintain a state of ketosis with greater dietary flexibility [40].

In a prospective intervention study by Nirmeen Adel Kiszk et al, the effect of a ketogenic diet on patients with drug-resistant epilepsy (DRE) was evaluated. The study included 80 patients, 40 of whom were assigned to the intervention group, where a ketogenic diet was introduced in addition to standard pharmacotherapy. After one month on a diet with a 2:1 fat-to-protein and carbohydrate ratio, participants in the intervention group were divided into two subgroups: A1 - continued the 2:1 diet, A2 - switched to a 3:1 diet. After three months, both subgroups showed a statistically significant reduction in the frequency and severity of epileptic seizures and an improvement in quality of life compared to the control group. The percentage of response to the diet was comparable in both groups, but the A1 group showed better acceptance of the taste of the diet, while the A2 group had higher lipid profile values [41].

In a randomized controlled trial involving 160 patients with DRE, the efficacy of the modified Atkins diet (MAD) was evaluated as an adjunct to standard drug therapy compared to pharmacotherapy alone. After 6 months, 26.2% of patients in the MAD with pharmacotherapy group compared to 2.5% in the drug-only group. In addition, quality of life was higher in the group using MAD. Side effects were few and included isolated cases of diarrhea and weight loss. This study confirmed that MAD can be an effective and well-tolerated support in the treatment of DRE.

A systematic review and meta-analysis conducted by Antonio Mutarelli et al, evaluated the efficacy of MAD as an adjunct to drug treatment in patients with drug-resistant epilepsy. Data from six randomized controlled trials involving a total of 575 patients were analyzed. It was shown that MAD significantly increased the percentage of patients with a seizure reduction of more than 50% and complete absence of seizures - in both children and adults - compared to the usual diet. Reported side effects were moderate and included constipation (17%), lethargy (11%) and anorexia (12%) [40].

Analyzed clearly indicate the effectiveness of the ketogenic diet, including the modified Atkins diet (MAD), as an adjunct to drug treatment in patients with drug-resistant epilepsy (DRE) in both children and adults. The diet was well tolerated, and reported side effects were mild to moderate in nature.

Conclusions

Drug-resistant epilepsy represents a major clinical challenge. It affects about 30% of patients with epilepsy. They fail to achieve seizure control despite treatment with at least two appropriately selected antiepileptic drugs (LEPs). Consequently, a multidirectional and individualized therapeutic approach is essential.

In cases where drug treatment proves ineffective, the method with the highest efficacy is surgical removal of the epileptic focus, especially in patients with well-localized lesions. Neurosurgery can lead to complete resolution of seizures and should be considered early in the treatment of drug-resistant epilepsy.

Alternatives for patients for whom resection surgery is not possible are neuromodulation methods. These include vagus nerve stimulation (VNS), deep brain stimulation (DBS) and responsive neurostimulation (RNS). These techniques, while not usually leading to a complete cure, significantly reduce seizure frequency and improve patients' quality of life. They are a valuable adjunct or alternative to surgical treatment.

In addition, the ketogenic diet is playing an increasingly important role in the treatment of drug-resistant epilepsy, especially in children, but also in adults. This diet, based on a high supply of fats and restriction of carbohydrates, can lead to a significant reduction in the number of seizures, au some patients - to their complete cessation. Although its use requires close medical and dietary supervision, it can be a valuable therapeutic option, especially when other methods are not available.

Modern treatment of drug-resistant epilepsy should be based on a comprehensive therapeutic model that combines pharmacotherapy, surgery, neuromodulation and dietary interventions. Individualization of therapy, interdisciplinary care and continuous development of medical technology offer a real chance to improve treatment outcomes and quality of life for patients with this difficult form of epilepsy.

Disclosures Author`s contribution:

Conceptualization: PF, WF, IK;

Methodology: GP, MS, JW, DK;

Software: PF, JW, PB, PK;

Check: WF, PK BN;

Formal analysis: PF, GP, IK;

Investigation: PF, KD, JW;

Resources: PB, GP, MS, DK;

Data curation: WF, IK, MS, KD;

Writing-rough preparation: PF, WF;

Writing-review and editing: PF, GP;

Visualization: WF, DK, PK;

Supervision: PF, IK;

Project administration: PF, WF

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REFERENCES

[1] Kwan P, Arzimanoglu A, Berg AT, Brodie MJ, Hauser WA, Mathern G, Moshe SL, Perucca E, Wlebe S, French J. Definition of drug resistant epilepsy: Cpmmision on Therapeutic Strategies, Special Report. Epilepsia 2009. http://doi.org10.1111/j.1528-1167.2009.02397.x

[2]Sabzvari T, Iqbal MA, Ranganatha A, Daher JC, Freire I, Maham S, Shamsi F, Anthony O.V.P, Hingorani AG, Sinha AS, Nazir Z, Shamsi F. A Comprehensive Review of Recent Trends in Surgical Approaches for Epilepsy Management. Cureus. 2024 Oct 17;16(10):e71715. PMID: 39553057. PMCID: PMC11568833. http://doi.org/10.7759/cureus.71715

[3] Schmitz B, Lattanzi S, Vonck K, Kalviainen R, Nashef L, Ben-Menachem E. Cenobamate in refractory epilepsy: Overview of treatment options and practical considerations. Epilepsia Open. 2023 Oct 3;8(4):1241–1255. PMID: 37743544. PMCID: PMC10690671. http://doi.org/10.1002,/epi4.12830

[4] Yang Y, Shangguan Y, Wang X, Liu R, Shen Z, Tang M, Jiang G. The efficacy and safety of third-generation antiseizure medications and non-invasive brain stimulation to treat refractory epilepsy: a systematic review and network meta-analysis study. Front Neurol 2024 Jan 9;14:1307296. PMID: 38264091. PMCID: PMC10804851 http://doi.org10.3389/fneur.2023.1307296

[5] Rola R.: The use of deep brain stimulation as an alternative treatment for drug-resistant epilepsy. Neurol Prakt 2012, 2(65), 7-10. Polish.

[6] Zhong C, Yang K, Wang N, Yang L, Yang Z, Xu L, Wang J, Zhang L. Advancements in Surgical Therapies for Drug-Resistant Epilepsy: A Paradigm Shift towards Precision Care. Neurol Ther. 2025 Feb 10;14(2):467–490. PMCID:PMC11906941 PMID: 39928287 http://doi.org10.1007/s40120-025-00710-4

[7] Goodale SE, González HFJ, Johnson GW, Gupta K, Rodriguez WJ, Shults R, Rogers BP, Rolston JD, Dawant BM, Morgan VL, Englot DJ. Resting-State SEEG May Help Localize Epileptogenic Brain Regions. Neurosurgery. 2019 Sep 16;86(6):792–801. PMCID: PMC7225010 PMID: 31814011. http://doi.org10.1093/neuros/nyz351

[8] Jehi L, Morita-Sherman M, Love TE, Bartolomei F, Bingaman W, Braun K, Busch R, Duncan J, Hader WJ, Luan G, Rolston JD, Schuele S, Tassi L, Vadera S, Sheikh S, Najm I, Arain A, Bingaman J,Diehl B,de Tisi J, Rados M, Van Eijsden P, Wahby S, Wang X, Wiebe S. Comparative Effectiveness of Stereo-EEG versus Subdural Grids in Epilepsy Surgery. Ann Neurol PMID: 34590337 PMCID: PMC9438788. http://doi.org10.1002/ana.26238

[9]Medina-Pizarro M, Spencer DD, Damisah EC. Recent advances in epilepsy surgery. Curr Opion Neurol. 2023 Apr 1;36(2):95-101. http://doi.org10.1097/WCO.0000000000001134

[10]Kerezoudis P, Parisi V, Marsh WR, Kaufman TJ, Lehman VT, Worrell GA, Miller KJ, Gompel JJV. Surgical Outcomes of Laser Interstitial Thermal Therapy for Temporal Lobe Epilepsy: Systematic Review and Meta-analysis. World Neurosurg. 2020 Nov:143:527-536.e3. PMID: 32750511. http://doi.org10.1016/j.wneu.2020.07.194

[11] Youngerman BE, Banu MA, Khan F, McKhann GM, Schevon CA, Jagid, Cajigas I ,Theodotou CB, Ko A, Buckley R, Ojemann JG, Miller JW, Laxton AW, Couture DE, Popli GS, Buch VP, Halpern CH, Le S, Sharan AD, Sperling MR, Mehta AD, Englot DJ, Neimat JS, Konrad PE, Sheth SA, Neal EG, Vale FL, Holloway KL, Air EL, Schwalb JM, D'Haese PF, Wu C. Long-term outcomes of mesial temporal laser interstitial thermal therapy for drug-resistant epilepsy and subsequent surgery for seizure recurrence: a multi-centre cohort study. J Neurol Neurosurg Psychiatry. 2023 Nov;94(11):879-886. PMID: 37336643 PMCID: PMC10776034. http://doi.org10.1136/jnnp-2022-330979

[12] Bottan JS, Almalki F, Nouri MN, Lau JC, Iansavichene AI, Gilmore G, Miller M, de Ribaupierre S, Andrade AV. Radiofrequency-thermocoagulation in pediatric epilepsy surgery: A systematic review and pooled analysis of cases. Seizure. 2025 Mar:126:6-13. PMID: 39874864. http://doi.org10.1016/j.seizure.2025.01.012

[13] Austelle CW, Cox SS, Wills KE, Badran B. Vagus nerve stimulation (VNS): recent advances and future directions. Clin Auton Res. 2024 Oct 4;34(6):529–547. PMID: 39363044. PMCID: PMC11543756 . http://doi.org10.1007/s10286-024-01065-w

[14] Gouveia FV, Warsi NM, Suresh H, Matin R, Ibrahim GM. Neurostimulation treatments for epilepsy: Deep brain stimulation, responsive neurostimulation and vagus nerve stimulation. Neurotherapeutic. 2024 Jan 4;21(3):e00308. PMID: 38177025. PMCID: PMC11103217. http://doi.org10.1016/j.neurot.2023.e00308

[15] Mandalaneni K, Rayi A. Vagus Nerve Stimulator. StatPearls Publishing. August 7, 2023

[16] Austelle CW, Cox SS, Wills KE, Badran B. Vagus nerve stimulation (VNS): recent advances and future directions. Clin Auton Res. 2024 Oct 4;34(6):529–547. PMID: 39363044. PMCID: PMC11543756. http://doi.org10.1007/s10286-024-01065-w

[17] Ben-Menachem E, Manon-Espaillat R, Ristanovic R, Wilder BJ, Mirza W, Tarver WB, Wernicke JF. Vagus nerve stimulation for treatment of partial seizures: 1. A controlled study of effect on seizures. First International Vagus Nerve Stimulation Study Group. Clinical Trial. 1994 May-Jun;35(3):616-26. PMID: 8026408.http://doi.org10.1111/j.1528-1157.1994.tb02482.x.
[18] Handforth A, DeGiorgio CM, Schachter SC, Uthman BM, Naritoku DK, Tecoma ES, Henry TR, Collins SD, Vaughn BV, Gilmartin RC, Labar DR, Morris 3rd GL, Salinsky MC, Osorio I, Ristanovic RK, Labiner DM, Jones JC, Murphy JV, Ney GC, Wheless JW. Vagus nerve stimulation therapy for partial-onset seizures: a randomized active-control trial. Clinical Trial. 1998 Jul;51(1):48-55. PMID: 9674777. http://doi.org10.1212/wnl.51.1.48.
[19] Scherrmann J , Hoppe C, Kral T, Schramm J, Elger CE. Vagus nerve stimulation: clinical experience in a large patient series. Clinical trial. 2001 Sep;18(5):408-14. PMID: 11709645. http://doi.org10.1097/00004691-200109000-00004.
[20] Jain P , Arya R. Vagus Nerve Stimulation and Seizure Outcomes in Pediatric Refractory Epilepsy: Systematic Review and Meta-analysis. Neurology. 2021 May 31;96(22):1041-1051 http://doi.org10.1212/WNL.0000000000012030
[21] Yang H, Shi W, Fan J, Wang X, Song Y, Lian Y, Shan W, Wang Q. Transcutaneous Auricular Vagus Nerve Stimulation (ta-VNS) for Treatment of Drug-Resistant Epilepsy: A Randomized, Double-Blind Clinical Trial. Neurotherapeutics. 2023 Mar 30;20(3):870–880. http://doi.org10.1007/s13311-023-01353-9
[22] Rola R. The use of deep brain stimulation as an alternative in the treatment of drug-resistant epilepsy. Neurol Prakt 2012, 2(65), 7-10
[23] Fabriba KA, Gupta V. Deep Brain stimulation. StatPearls. July 24, 2023
[24] Salanova V, Witt T , Worth R, Henry TR , Gross RE, Nazzaro JM , Labar D , Sperling MR , Sharan A , Sandok E, Handforth A, Stern JM , Chung S , Henderson JM , French J , Baltuch G , Rosenfeld WE , Garcia P , Barbaro NM , Fountain NB , Elias WJ , Goodman RR , Pollard JR , Tröster AI , Irwin CP , Lambrecht K , Graves N , Robert Fisher , SANTE Study Group. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Randomized Controlled Trial, Neurology. 2015 Mar 10;84(10):1017-25. PMID: 25663221. PMCID: PMC4352097. http://doi.org10.1212/WNL.0000000000001334.
[25] Gouveia FV, Warsi NM, Suresh H, Matin R, Ibrahim GM. Neurostimulation treatments for epilepsy: Deep brain stimulation, responsive neurostimulation and vagus nerve stimulation. Neurotherapeutics. 2024 Jan 4;21(3):e00308. PMID: 38177025. PMCID: PMC11103217. http://doi.org10.1016/j.neurot.2023.e00308

[26] Salanova V, Witt T , Worth R, Henry TR , Gross RE, Nazzaro JM , Labar D , Sperling MR , Sharan A , Sandok E, Handforth A, Stern JM , Chung S , Henderson JM , French J , Baltuch G , Rosenfeld WE , Garcia P , Barbaro NM , Fountain NB , Elias WJ , Goodman RR , Pollard JR , Tröster AI , Irwin CP , Lambrecht K , Graves N , Robert Fisher , SANTE Study Group. Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Randomized Controlled Trial, Neurology. 2015 Mar 10;84(10):1017-25. PMID: 25663221. PMCID: PMC4352097. http://doi.org10.1212/WNL.0000000000001334.
[27] Salanova V, Sperling MR , Gross RE , Irwin CP , Vollhaber JA , Giftakis JE, Fisher RS. The SANTÉ study at 10 years of follow-up: Effectiveness, safety, and sudden unexpected death in epilepsy. Randomized Controlled Trial, Epilepsy. 2021 Jun;62(6):1306-1317. PMID: 33830503.\ http://doi.org10.1111/epi.16895
[28] Kaufmann E, Peltola J , Colon AJ , Lehtimäki K , Majtanik M, Mai JK, Bóné B, Bentes C, Coenen V, Gil-Nagel A, Goncalves-Ferreira AJ, Ryvlin P, Taylor R, Brionne T, Gielen F, Song S, Boon P; MORE study group. Long-term evaluation of anterior thalamic deep brain stimulation for epilepsy in the European MORE registry. Epilepsja. 2024 Aug;65(8):2438-2458. http://doi.org10.1111/epi.18003.
[29] Raslan EE, Al-Hawas SF, Alghamdi MM, Alblwan AS, Alhomaidhi A, Alruwaili AA, Warar R, Alhwaiti AS, Alsubhi RM, Al-harbi WF, Alasmari MN. Assessment of the Efficacy of Deep Brain Stimulation (DBS) in Managing Drug-Resistant Epilepsy (DRE): A Systematic Review and Meta-Analysis of Randomized Controlled Trials (RCTs). Cureus. 2024 Oct 13;16(10):e71348. PMCID: PMC11555489 PMID: 39534832. http://doi.org10.7759/cureus.71348
[30] Gouveia FV, Warsi NM, Suresh H, Rafi Matin R, Ibrahim GM. Neurostimulation treatments for epilepsy: Deep brain stimulation, responsive neurostimulation and vagus nerve stimulation. Neurotherapeutics. 2024 Jan 4;21(3):e00308. PMCID:PMC11103217 PMID: 38177025 http://doi.org10.1016/j.neurot.2023.e00308
[31] Mushtaq O, Grezenko H, Rehman A, Sher H, Sher Z, Kaakyire DA, Hanifullah S, Dabas M, Saleh G, Shehryar A, Khan I. Role of Responsive Neurostimulation in Managing Drug-Resistant Epilepsy: A Systematic Review of Clinical Outcomes. Cureus. 2024 Aug 28;16(8):e68032. PMCID:PMC11431993 PMID: 39347167. http://doi.org10.7759/cureus.68032
[32] Jarosiewicz B, Morell M. The RNS System: brain-responsive neurostimulation for the treatment of epilepsy. Expert Review of Medical Devices. 24 May 2019, Accepted 18 Oct 2019. https://doi.org/10.1080/17434440.2019.1683445

[33] Ghosh S, Sinha JK, Ghosh S, Sharma H, Bhaskar R, Narayanan KB. A Comprehensive Review of Emerging Trends and Innovative Therapies in Epilepsy Management. Brain Sci. 2023 Sep 11;13(9):1305. PMCID: PMC10527076 PMID: 37759906 http://doi.org10.3390/brainsci13091305

[34] Kusyk D, Meinert J, Stabingas KC, Yin Y, Whiting AC. Systematic Review and Meta-Analysis of Responsive Neurostimulation in Epilepsy. Meta-Analysis, Word Neurosurg. 2022 Nov:167:e70-e78. PMID: 35948217. http://doi.org10.1016/j.wneu.2022.07.147

[35] Yang Y, Wei P, Shi J , Mao Y, Zhang J, Ding Lei [4], Yang Z , Song S , Qian R , Li W, Shan Y , Zhao G. Early assessment of responsive neurostimulation for drug-resistant epilepsy in China: A multicenter, self-controlled study. Randomized Controlled Trial, Chin Med. J. 2025 Feb 20;138(4):430-440. PMID: 39593204PMCID: PMC11845213. http://doi.org10.1097/CM9.0000000000003292

[36] Levy AS, Bystrom LL, Brown EC, Fajardo M, Wang S. Responsive neurostimulation for treatment of pediatric refractory epilepsy: A pooled analysis of the literaturę. Clin Neurol Neurosurg. 2023 Nov:234:108012. PMID: 37839147. http://doi.org10.1016/j.clineuro.2023.108012.

[37] Panov F, Ganaha S, Haskell J , Fields M, Vega-Talbott ML, Wolf S , McGoldrick P , Marcuse L, Ghatan S. Safety of responsive neurostimulation in pediatric patients with medically refractory epilepsy. J Neurosurg Pediatr. 2020 Nov 5;26(5):525-532. http://doi.org10.3171/2020.5.PEDS20118.

[38] Zhou C, Wang M , Liang J, G. G[4], Ning Chen. Ketogenic Diet Benefits to Weight Loss, Glycemic Control, and Lipid Profiles in Overweight Patients with Type 2 Diabetes Mellitus: A Meta-Analysis of Randomized Controlled Trails. Int J Environ Res Public Health. 2022 Aug 22;19(16):10429. PMCID: PMC9408028 PMID: 36012064. http://doi.org10.3390/ijerph191610429

[39] Ghosh S, Sinha JK, Ghosh S, Sharma H, Bhaskar R, Narayanan KB. A Comprehensive Review of Emerging Trends and Innovative Therapies in Epilepsy Management. Brain Sci. 2023 Sep 11;13(9):1305. PMCID:PMC10527076 PMID: 37759906. http://doi.org10.3390/brainsci13091305

[40] Mutarelli A, Nogueira A, Felix N, Dagostin KS, Martins Castro LH, Mota Telles JP. Modified Atkins diet for drug-resistant epilepsy: A systematic review and meta-analysis of randomized controlled trials. Seizure, 2023 Nov:112:77-83. PMID: 37769548. http://doi.org10.1016/j.seizure.2023.09.010.

[41] Kishk NA, Yousof HZ, Ebraheim AM, Ali Elkholy TA, Soliman SH, Mohammed RA, Shamloul RM. The effect of ketogenic diet escalation in adolescents and adults with drug-resistant epilepsy: a prospective study. Nutr Neurosci. 2022 Oct;25(10):2023-2032. http://doi.org10.1080/1028415X.2021.1927604

[42] Manral M, Dwivedi R, Gulati S, Kaur K, Nehra A, Pandey RM, Upadhyay AD, Sapra S, Tripathi M. Safety, Efficacy, and Tolerability of Modified Atkins Diet in Persons With Drug-Resistant Epilepsy: A Randomized Controlled Trial. Neurology. 2023 Mar 28;100(13):e1376-e1385. PMID: 36599697 PMCID: PMC10065201. 2023 Mar 28;100(13):e1376-e1385. http://doi.org10.1212/WNL.0000000000206776