PERSPECTIVE

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Future of epilepsy treatment: integration of devices

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ABSTRACT The use of devices in the treatment of epilepsy is an emerging therapy for those patients whose seizures are not controlled by medications. This article will discuss current treatment options with devices for vagus nerve stimulation, deep brain stimulation and responsive neurostimulation. Emerging therapies in noninvasive neurostimulation such as with trigeminal nerve stimulation, transcranial magnetic stimulation and transcranial direct current stimulation may prove to be promising solutions. Finally, new and enhanced techniques of drug delivery are discussed as well as other devices with potential use in the study and treatment of epilepsy.

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Evaluate the benefits and risks associated with use of the vagus nerve stimulator
- Describe responsive neurostimulation in the treatment of epilepsy
- Describe deep brain stimulation in the treatment of epilepsy
- Discuss potential emerging treatments of epilepsy

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KEYWORDS

- DBS • DCS • devices
- medically intractable
- epilepsy • RNS • TMS • TNS
- VNS

Indications

Approximately 30% of patients with epilepsy remain intractable despite multiple anti-epileptic medication trials [1,2]. In these patients, other treatment options such as resective surgery or a disconnection procedure, such as palliative corpus callosotomy, are often necessary. In medically intractable partial epilepsy, no other intervention, including the use of devices is as effective as resective epilepsy surgery in achieving seizure freedom in appropriately selected patients. In a controlled, prospective study of patients with temporal lobe epilepsy, 59% became seizure free after temporal lobectomy compared with only 8% in the medical management arm [3]. Retrospective studies show seizure freedom rates between 56 and 83% in patients with temporal epilepsy following temporal lobectomy [3–6]. Those with mesial temporal onset had better outcomes than those with neocortical onset, and though seizure freedom declined slightly over time, the rate of freedom remained above 55% [4,5]. Seizure freedom rates are similar in nonlesional temporal lobe epilepsy and though less favorable in extratemporal epilepsy with only 13–47% seizure freedom, surgery often remains the only option for patients after all other non-surgical options have failed [7–9].

However, epilepsy surgery is not always possible. Patients with generalized seizures, seizures emanating from both hemispheres, and those with a seizure onset zone in eloquent cortex such as motor or language areas are often not surgical candidates. Further, patients that have already undergone respective epilepsy surgery but continue to remain intractable are often poor candidates for further resection. In these patients,

more innovative therapies are needed and currently, one such option comes in the form of epilepsy devices. These devices currently include vagus nerve stimulation and responsive brain stimulation, as well as deep brain stimulation. Ongoing studies include trigeminal nerve stimulation, transcranial and transcutaneous stimulation, magnetic stimulation and potential new mechanisms for direct drug delivery to the brain.

Current available devices**• Vagus nerve stimulator**

The vagus nerve stimulator (VNS) has been in use since the mid-1990s and is a well-established option in those patients that are unable to undergo surgery. The device is implanted pectorally on the left with leads connecting to the left vagus nerve at the carotid bifurcation. Stimulation is usually initiated 2 weeks after implantation and is delivered in an on-off fashion with the ability to adjust the output current, signal frequency, signal pulse width and signal on and off times. Special magnet-activated stimulus parameters, often with a higher output current, can be triggered with the placement of a magnet briefly over the device by the patient or caregiver. This has been shown to shorten or abort seizures, decrease their intensity and decrease the recovery period [10].

In most practices, the target range of stimulation is between 1.25 and 2.00 mA with early randomized controlled studies establishing a direct relationship between stimulation intensity and seizure frequency reduction [11]. Changes to signal frequency and pulse width are often manipulated to control side effects and increase battery life [12]. If standard programming is not effective, the option of rapid cycling (term used to describe

a high duty cycle) is available, though this results in faster depletion of the normal expected battery life of 5–10 years [13,14]. Various mechanisms have been proposed such as increased norepinephrine excretion in the locus coeruleus, increased firing of the serotonergic neurons in the dorsal raphe nucleus, immunomodulation by effecting hippocampal plasticity or by increasing arousal via activation of the reticular activating system [15–17].

There are no head-to-head controlled studies comparing VNS with medication trials. Pre-market trials comparing high and low frequency stimulation in 194 and 114 patients over 12 to 16 weeks found a mean seizure reduction of 27.9 and 24.5% in the high stimulation group compared with the low stimulation (15.2 and 6.1%) as well as a 50% responder rate of 23.4 and 31% in the high stimulation group compared with 15.7 and 13% in the low stimulation group [18,19]. With long-term use, studies have demonstrated that approximately half of patients will have a greater than 50% reduction in their seizure frequency after implantation with relatively few (less than 10%) becoming seizure free [13,18,20–22]. These long-term studies are flawed by patient attrition, as the effect of VNS has been shown to increase with time [18,20,22–23]. VNS therapy is equally effective in children as demonstrated by a 57.9% seizure reduction in 128 patients with 64.8% of those children achieving greater than 50% reduction during the mean follow-up time of 5.3 years [24]. There have been no studies thus far investigating who are the best responders to VNS, however, those with focal epilepsies seem to do better than those with generalized epilepsies [21].

Overall, VNS therapy is well tolerated. There is a small operative risk with implantation encompassing mainly hemorrhage and infection. Very rarely there can be damage to the carotid artery or laryngeal nerve. The most cited adverse effects with VNS therapy are hoarseness, coughing and dyspnea usually occurring during the ‘on’ time [21]. Side effects decrease over time [21]. Other less common adverse effects include worsening of sleep apnea as well as dysarthria and/or dysphagia [16,25]. Patients and caregivers report increased alertness, shortened seizure duration and increased mood with VNS therapy which can lead to antiepileptic drug medication reduction and to treatment in those with depression [26–31]. The VNS device is MRI compatible using certain coils if the signal frequency is reduced to 0.0 mA for obtaining brain scans. MRI imaging

of the spine cannot be performed with the leads in place.

Transcutaneous activation of the vagus nerve has been utilized and studied via electroacupuncture which has inspired development of transcutaneous vagus nerve stimulator devices [32]. Nemos®, manufactured by Cerbomed (Erlangen, Germany), is a transcutaneous device which stimulates the auricular branch of the vagus nerve and which received the CE mark in Europe with early favorable results in a small cohort study [33]. However, larger studies are still needed. Other transcutaneous devices currently being studied in the treatment of epilepsy include gammaCore® (ElectroCore Medical LLC, NJ, USA), which has been approved for headache treatment in Europe, and Cerbomed’s Transcutaneous Vagus Nerve Stimulation (t-VNS®) [34,35]. Cyberonics (TX, USA) announced early results at the American Epilepsy Society in December 2013 of the E-36 study of their AspireSR™ generator which combines traditional VNS therapy with seizure detection technology via changes in cardiac rhythms to create a closed-loop, responsive stimulation device [36]. The AspireSR generator received the CE mark in Europe in February 2014.

• Responsive neurostimulation

Responsive neurostimulation (RNS) as a treatment for epilepsy was developed after direct electrical cortical stimulation was shown to terminate after-discharges, a model of epileptiform activity and focal seizures [37]. The RNS® (NeuroPace, CA, USA) is the first closed-loop system developed, tested, and US FDA approved in the treatment of epilepsy. The device is able to detect abnormal electrical activity and then deliver electrical stimulation to the same area as a method of preventing seizures. The RNS was given FDA approval in the USA in November 2013 and is the only responsive stimulation device approved for clinical use.

Treatment with the RNS system is ideal for the patient with either focal epilepsy that is otherwise unable to undergo epilepsy surgery or the patient with multifocal epilepsy with no more than two discrete epileptic onset zones. Up to two leads containing four electrodes each, utilizing implantable depth and/or cortical strip electrodes, can be placed into/over the epileptogenic zone (**Figure 1**). The leads are connected to the device which is implanted in the skull. The device continuously records and processes intracranial EEG data obtained from the placed leads and

stores up to 30 min of EEG activity. The patient is required to interrogate the device with a remote monitor frequently and more importantly, after seizures. The data are transferred online to a secure patient data management system. The data can be reviewed and monitored by the physician and seizure detection algorithms can be tested. This data are utilized to program the device to the individual patient's seizure onset pattern. When the device detects a seizure, it is programmed to deliver up to five individual pulses of stimulation. The stimulation depends on seizure onset location and electrode configuration. The signal pulse width is set between 160 and 200 μ s with the signal frequency and duration set at 100–200 Hz and 100 ms, respectively. The expected battery life is between 2.5 and 4 years [38].

In the RNS System Pivotal Clinical Investigation, a total of 191 patients were studied in a randomized control trial with a blinded period of 12 weeks followed by an open-label period of 84 weeks [39]. The seizure reduction

over the entire blinded observation period was 37.9% in the treatment group versus 17.3% in the control group ($p = 0.012$) with overall seizure reduction at the end of the 3-month blinded period of 41.5% in the treatment arm and 9.4% in the control ($p = 0.008$). However, there was no difference between the groups in percentage of patients that achieved a greater than 50% reduction in seizure frequency [39]. Long-term responses increased with prolonged use as seen with VNS. At 5 years, median seizure reduction was greater than 65% with approximately 15% of patients achieving seizure freedom [35,36]. A 2-year follow-up study found no difference between patients with mesial temporal lobe epilepsy and nonmesial temporal lobe epilepsy (mean seizure reduction of 55 and 58%, respectively) but that patients with a single seizure focus did better overall all than those with multifocal epilepsy [40].

RNS is well tolerated with low major operative risks including nonclinical serious intracranial hemorrhage (2.1%) and infection (5.2%). More common adverse symptoms included headache and pain at the implantation site [39]. There were no adverse effects on mood inventories or neuropsychological measures at the end of the blinded period or at 2 years out. In fact, there was an actual improvement in verbal functioning, visuospatial ability and memory at both 1 and 2 years follow-up in the RNS patients [39]. MRI of the brain with the RNS system in place is not advisable as there is intense artifact from the device and further, there is a theoretical risk for lead heating.

• Deep brain stimulation

Deep brain stimulation (DBS) has been studied and explored for many years. The thalamus has been a popular site of stimulation due to its connections to the limbic system and role in initiation of generalized seizures and propagation of partial seizures [41,42]. Besides the thalamus, other targeted areas have included the caudate nucleus [43], the subthalamic nucleus [44], the locus coeruleus [45], the cerebellum [46–49] and the hippocampus [50,51]. Cerebellar stimulation has not been effective, but hippocampal stimulation has been promising in early studies [50–52]. The CoRaStiR trial is ongoing and compares medial temporal lobe resection with amygdala/hippocampal stimulation and sham stimulation [53].

Thalamic targets for stimulation have included the anterior nucleus, the centromedian

Figure 1. Different implantations for RNS®. (A & B) Implantation of depth electrodes in the bilateral hippocampi demonstrated by CT scan of the head on the left and axial T2 FLAIR MRI on the right. On the CT scan, you can also see the RNS (responsive neurostimulation) recording and stimulation device that is implanted in the skull. (C) CT scan showing implantation using grid electrodes for neocortical stimulation of the left lateral temporal language area. Only eight contacts on two leads are connected. (D) CT scan showing implantation of a depth electrode in the hippocampus and an electrode strip over the lateral temporal neocortex.

nucleus [54], the mediodorsal nucleus [55] and the ventroposterolateral nucleus [56]. Stimulation in the centromedian nucleus was initially thought to be effective in epilepsy. In early uncontrolled studies, seizure reduction was measured between 80 and 100% with the additional benefit of normalization of the EEG and improvements in psychological outcomes [54]. However, when these results were followed up with a double-blind pilot study, seizure reduction rates were measured at only 30% without statistical significance between the stimulated group and the control group [57].

Besides various cohort studies, there has been only a single randomized controlled trial with sufficient sample size for thalamic stimulation in epilepsy. The SANTE trial randomized 110 patients into a stimulation group versus a sham group. Implantation utilized the same DBS device that is used in Parkinson's disease with the following settings: 5 V amplitude, 90 μ s pulse width, 140 Hz frequency and 1 min on/5 min off targeted at the anterior nucleus (Figure 2). Median seizure reduction at the end of the 3-month observation period was 29% in the stimulation group compared with 17% in the control group [58]. This was considered statistically significant using a generalized estimating equation ($p = 0.038$). However, as with the other neurostimulation modalities, improvement was seen over the long term. At the end of 3 months, median seizure reduction was 40.5% in the stimulated group compared with 14.5% in the control group [58]. At 1-, 2- and 5-year follow-up, the efficacy improved further with a median seizure reduction of 69% and 16% of patients achieving seizure freedom [59]. Further, those patients with temporal lobe epilepsy seemed to respond better than patients with extratemporal or neocortical epilepsy [58]. A follow-up study looking at recruitment rhythm comparisons between responders and nonresponders was undertaken, but no results have been generated as yet (SANTE-RR) [60]. Over the long term, approximately 16% of patients withdrew from the study. There were no symptomatic intracranial hemorrhages but 4.5% of patients had hemorrhages detected by imaging. The most common serious side effect was infection, either at the generator or lead site, which occurred in 12.7% of patients. These were all successfully treated. Finally, patients in the stimulated group reported more cognitive and depressive symptoms, though this was

Figure 2. Placement of deep brain stimulation electrodes in the anterior nucleus of the thalamus.

not statistically significant. The average battery life was around 3 years and the device is not compatible with MRI [58]. The device has the CE mark in Europe but was not approved by the FDA in the USA when presented in 2010. There were concerns at that time that the 3-month blinded-period of the SANTE trial was too short to adequately study the device. Now that long-term use data continues to show positive results in the treatment of epilepsy, we are hopeful that DBS will become available in the USA.

Noninvasive stimulation: an emerging practice

Neurostimulation is an established treatment of epilepsy and has shown to be effective. It opens up an additional treatment venue to patients who are not candidates for epilepsy surgery. Emerging therapies are focused on other modes of stimulation and especially noninvasive stimulation. There are several models of noninvasive vagus nerve stimulators as mentioned earlier. Other noninvasive neurostimulation devices include transcutaneous trigeminal nerve stimulation (tTNS or TNS), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

NeuroSigma (CA, USA) has manufactured the Monarch™ eTNS™, which utilizes an external removable single gel electrode applied to the forehead to transcutaneously stimulate the trigeminal nerve. The device is recommended to be worn a minimum of 12 h per day, or overnight while sleeping, and delivers an on/off stimulation pattern similar to VNS to the

bilateral orbital and supratrochlear branches of the trigeminal nerve. The theorized mechanism involves activation of the ascending reticular activating system through sensory nerve input (via the trigeminal nerve in this case) to cause desynchronization by way of widespread cortical projections [61]. Tentatively, any sensory nerve could be used under this mechanism barring autonomic disruption. The Phase II study with 50 patients treated over 18 weeks was recently completed using the following parameters: 2 Hz stimulation frequency, 2 s on and 90 s off duty cycle with a pulse width of 50 μ s. Median seizure reduction over the entire 18-week period was 16.1% reduction in the treatment group and 8.0% in the control group with 30.2% of patients in the treatment group achieving greater than 50% reduction compared with 21.1% in the control group [62]. This was not clinically significant. However, at the end of the 18-week period, there was a significant difference in the 50% responder rate of 40.5% in the treatment group compared with 15.6% in the control group ($p = 0.078$) [62]. Longer follow-up may reveal further widening between the two groups. Overall, the eTNS system is well tolerated with only minor side effects including anxiety, headache and skin irritation as the most common finding [63]. Further, there was a significant improvement in mood as measured with the Beck Depression Inventory in the treatment group [62]. The major advantage with TNS is that it is external, does not require surgical placement and is easily discontinued if intolerable or ineffectual. A Phase III study is currently being planned which will hopefully give us more information on this emerging therapy [64].

Repetitive TMS (rTMS or TMS) has been studied for over 20 years and functions via an electric coil placed over the scalp using rapidly changing magnetic fields to induce current changes in the brain [65]. It has been shown to reduce cortical excitability and reduce interictal epileptiform activities [66]. Animal models showed that TMS blocked seizures from occurring [67]. Human studies have had mixed results. Initially, TMS was being applied at the vertex without individualization for seizure onset zone. These studies showed negligible changes in seizure frequency with results being minimal and brief [68–70]. More recent studies have focused on patients with focal and multifocal epilepsies with TMS administered focally to each individual's epileptogenic zones which has produced better results [68,71–74]. A

randomized controlled trial of 21 patients with cortical dysplasias underwent localized TMS or sham stimulation with follow-up at 60 days. The treatment group had 58% mean seizure reduction compared with no significant change in the sham group ($p < 0.0001$). Eight-three percent of the treatment group achieved a greater than 50% reduction in mean seizure frequency while none of the nine patients in the sham group did [74]. There are two active studies currently recruiting for multifocal and unifocal refractory epilepsy. TMS may also improve mood [75]. Effects on cognition are mixed and likely associated with the mood effects [76].

tDCS works by direct electrical stimulation on the scalp over the area of interest via electrodes which can in turn induce either hyperexcitability or hypoexcitability of the cortex depending on the type of stimulation. This type of stimulation has been studied and used regularly in neurorehabilitation and is being studied in psychiatric disorders. Cathodal stimulation of the epileptogenic zone to decrease neuronal excitability has only been recently studied in epilepsy patients. A randomized control trial of 19 patients with medically refractory focal and multifocal epilepsy who underwent a single 20-min session of tDCS found a reduction in interictal epileptiform discharges and had an approximate 40% reduction in mean seizure frequency at 1-month follow-up compared with no change in the sham stimulation group [77]. Further studies in patients with refractory focal onset seizures are ongoing [78].

Drug delivery devices

Another emerging therapy using devices is aimed at enhanced delivery of antiepileptic medications. Intrathecal and intraventricular drug delivery bypass the blood–brain barrier and thus enhance pharmacological activity in the brain as well as limit systemic effects of administered medications [79]. Transmeningeal delivery of antiepileptic agents requires a constant infusion and would be most effective in neocortical epilepsies [80,81]. All of these methods, however, are still untar-geted in that normal brain tissue is still exposed to the antiepileptic agent. More targeted methods include direct intracerebral delivery of therapeutic agents via a catheter placed directly into the epileptic zone [82–84]. This method is limited by a nonuniform diffusion of therapeutic agents which reduces control of the therapy. A possible solution has arisen in convection-enhanced

delivery. This process administers drug by slow infusion under positive pressure and results in a larger volume of distribution as well as a more uniform distribution of the therapeutic agent than what is achieved by diffusion methods. Additionally, with convection-enhanced delivery, the target of drug delivery has a sharply defined border which results in more refined focalized treatment [85]. Early animal studies have been promising [86,87]. Finally, there have been several animal studies dedicated to the production of drug-eluting wafers that could be implanted intracranially at the site of epileptogenesis [88,89]. This method provides the same benefits as with the previous methods but would be limited in the need for repeat craniotomies to replenish the wafer. There are no active human clinical trials involving any of these methods at this time.

Other devices

These nonstimulation, nonpharmacological devices provide yet another mechanism for epilepsy treatment. Cold water applied directly to the brain in the operating room and induced hypothermia in comatose patients have both been shown to stop seizures [90]. In animal models, focal brain cooling has demonstrated an inhibition in epileptic kindling as well as an increased threshold for chemically induced seizures [91,92]. Focal, passive cooling in rats after traumatic brain injury as little as 2°C has been shown to prevent chronic recurrent seizures [93]. The development of an external device to cool the head and neck and thereby the brain is currently being studied as well as implantable devices for focal cooling in patients with focal epilepsy [94]. Other ideas evolve around the use of a partial re-breather wherein the theory is that the induced respiratory acidosis by re-breathing exhaled gases would cause a drop in systemic pH that would stop or prevent seizure activity [95].

Other epilepsy devices have aimed at seizure detection/alerting systems. These would be especially important in the study and prevention of sudden unexpected death in epilepsy (SUDEP). These devices employ monitoring of electromyography data, eye and muscle movements, and body vibrations with the use of electrodes, accelerometers, and bed alarms to name a few [96,97]. NeuroVista (WA, USA) had completed early human studies on their implanted wireless device that continuously records and analyzes intracranial EEG data, however, the company is no longer active [98]. Through all of these

methods, the acquired data are being used to design computer models that could potentially predict seizures. Seizure prediction would be invaluable to the patient but also to understanding of seizure behavior and pathogenesis. If seizures could be adequately predicted, treatments and lifestyle could be tailored to seizure occurrence.

Conclusion

The use of devices in the treatment of epilepsy is a growing field. Currently, only two devices (VNS and RNS) are approved for use in the USA and while deep brain stimulation has not been approved in the USA it had been approved for treatment of epilepsy in Europe and over 30 different countries. While epilepsy surgery remains the mainstay of treatment for medically intractable epilepsy, this may not always be true in the future. The use of devices avoids the functional deficits of epilepsy surgery, minimizes the need for antiepileptic medications and their potential side effects and at the same time is more inclusive to all epilepsy types, such as generalized epilepsies, focal epilepsies involving eloquent cortex or even patients who previously had epilepsy surgery but continue to have intractable seizures. The development of devices to treat epilepsy is difficult, especially in neurostimulation. It is clear that current animal models are not representative [54]. Additionally, the number of variables included with stimulation, in other words, pulse width, frequency and duty cycle, among others, can be overwhelming. Performing blinded studies can be difficult and costly.

With few current options, the use of devices for the treatment of epilepsy has been limited. However, with the recent FDA approval of RNS and with so many more devices on the horizon, the use of devices in treatment of epilepsy is likely to become much more prominent.

Future perspective

This article outlines currently available devices used in the treatment of epilepsy as well as devices that are currently in development. We predict that in the next several years, DBS will be approved for use in the USA, the use of RNS will be well established, and at the same time, transcutaneous TNS should be introduced to the market. While several different devices are under development, convection-enhanced drug delivery seems especially promising.

EXECUTIVE SUMMARY

Currently available devices

- Vagus nerve stimulator, responsive nerve stimulator and deep brain stimulator.

Devices in development

- Neurostimulation: trigeminal nerve stimulation, transcranial magnetic stimulation and transcranial direct current stimulation.
- Drug delivery: convection-enhanced delivery.
- Other: cooling devices, seizure detection and seizure alarm systems.

Future studies involving devices

- Improved closed loop systems that detect and treat seizures without external intervention.
- Better animal models.
- Longer studies.
- Better understanding of device stimulation parameters.

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• of interest; •• of considerable interest

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Future of epilepsy treatment: integration of devices

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. You are seeing a 30-year-old man referred to your clinic for partial epilepsy with epileptogenic foci in both temporal lobes. He has experienced failure of several trials with medical therapy. You consider that he may be a candidate for an implanted device to treat his epilepsy. What should you consider regarding the vagus nerve stimulator (VNS)?

- ☐ A Stimulation intensity does not correlate well with seizure control
- ☐ B Approximately one-half of patients experience a long-term reduction in seizures of 50% or more
- ☐ C VNS is usually preferred for patients with generalized vs focal epilepsy
- ☐ D The main adverse effects of VNS include fatigue and depression

2. Which of the following statements regarding responsive neurostimulation (RNS) is most accurate?

- ☐ A The RNS system is ideal for patients with multifocal epilepsy
- ☐ B Generally, RNS does not require patient input or activity
- ☐ C The expected battery life of RNS is 10 years
- ☐ D Long-term responses are superior to short-term results in RNS

3. You also consider whether to initiate deep brain stimulation (DBS). What should you consider regarding this treatment?

- ☐ A The most effective brain area to target is the centromedian nucleus
- ☐ B DBS has been approved in Europe but not the United States
- ☐ C Patients with extratemporal epilepsy are most likely to respond
- ☐ D The most common serious adverse effect of DBS is intracranial hemorrhage

4. What can you tell this patient about other emerging treatments of epilepsy?

- ☐ **A** The transcutaneous trigeminal nerve stimulation system is meant to be worn at least 12 hours per day
- ☐ **B** Transcranial magnetic stimulation should be applied at the vertex without specific targets
- ☐ **C** Transmeningeal drug delivery allows for periodic drug infusion
- ☐ **D** Transcranial direct current stimulation has not been demonstrated to reduce seizure frequency