A systematic review of deep brain stimulation for the treatment of drug-resistant epilepsy in childhood

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OBJECTIVE Drug-resistant epilepsy (DRE) presents a therapeutic challenge in children, necessitating the consideration of multiple treatment options. Although deep brain stimulation (DBS) has been studied in adults with DRE, little evidence is available to guide clinicians regarding the application of this potentially valuable tool in children. Here, the authors present the first systematic review aimed at understanding the safety and efficacy of DBS for DRE in pediatric populations, emphasizing patient selection, device placement and programming, and seizure outcomes.

METHODS The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and recommendations. Relevant articles were identified from 3 electronic databases (MEDLINE, Embase, and Cochrane CENTRAL) from their inception to November 17, 2017. Inclusion criteria of individual studies were 1) diagnosis of DRE; 2) treatment with DBS; 3) inclusion of at least 1 pediatric patient (age $\leq$ 18 years); and 4) patient-specific data. Exclusion criteria for the systematic review included 1) missing data for age, DBS target, or seizure freedom; 2) nonhuman subjects; and 3) editorials, abstracts, review articles, and dissertations.

RESULTS This review identified 21 studies and 40 unique pediatric patients (ages 4–18 years) who received DBS treatment for epilepsy. There were 18 patients with electrodes placed in the bilateral or unilateral centromedian nucleus of the thalamus (CM) electrodes, 8 patients with bilateral anterior thalamic nucleus (ATN) electrodes, 5 patients with bilateral and unilateral hippocampal electrodes, 3 patients with bilateral subthalamic nucleus (STN) and 1 patient with unilateral STN electrodes, 2 patients with bilateral posteromedial hypothalamus electrodes, 2 patients with unilateral mammillothalamic tract electrodes, and 1 patient with caudal zona incerta electrode placement. Overall, 5 of the 40 (12.5%) patients had an International League Against Epilepsy class I (i.e., seizure-free) outcome, and 34 of the 40 (85%) patients had seizure reduction with DBS stimulation.

CONCLUSIONS DBS is an alternative or adjuvant treatment for children with DRE. Prospective registries and future clinical trials are needed to identify the optimal DBS target, although favorable outcomes are reported with both CM and ATN in children.

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KEYWORDS DBS; epilepsy; children; functional neurosurgery

DRUG-RESISTANT epilepsy is a complex condition that may be treated surgically using a wide range of procedures in the appropriately selected patient. These include resections and ablative surgery, functional disconnections, and neuromodulation. In children, surgical treatments are increasingly emphasized given the

medical and psychosocial burden of drug-resistant epilepsy (DRE)²² and the detrimental effects of seizures and medications on the developing brain.¹⁶ The Early Randomized Surgical Epilepsy Trial provided class I evidence for the benefit of early resection¹¹ compared with medical management in adolescents with temporal lobe epilepsy.

ABBREVIATIONS ATN = anterior thalamic nucleus; CM = centromedian nucleus of the thalamus; DBS = deep brain stimulation; DRE = drug-resistant epilepsy; RNS = responsive neurostimulation; STN = subthalamic nucleus; VNS = vagus nerve stimulation.

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Furthermore, a single-center randomized controlled trial of children younger than 18 years with DRE demonstrated a 77% seizure freedom for surgical treatment compared with 7% for medical treatment.¹⁰ In patients without localization-related epilepsy or unacceptable iatrogenic risk to eloquent cortex, neuromodulation may decrease the seizure burden and improve quality of life.³¹ Vagus nerve stimulation (VNS) is a viable outcome with long-term seizure reduction,³¹ although complications such as hardware failure, deep infection, hoarseness, dysphasia, and torticollis have been described in children.³⁶ The responsive neurostimulation (RNS) system was approved by the FDA in 2003 for use in patients 18 years or older with DRE. Studies have demonstrated that adults can benefit from moderate seizure reduction,^{14,17} but this new therapy has not yet been thoroughly studied in children.

Deep brain stimulation (DBS) is a therapeutic option that delivers electrical stimulation in order to modulate cortical excitability, thereby reducing the frequency and severity of seizures in an adjustable and reversible manner. The SANTE (Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy) trial demonstrated statistically significant reductions in seizure frequency in a multicenter prospective randomized cohort of 110 adults with DRE who underwent anterior nucleus DBS.¹² Several DBS targets have been studied,⁸ including the anterior thalamic nucleus (ATN) for patients with frontotemporal epilepsy,^{21,27,32} the centromedian nucleus of the thalamus (CM) for patients with generalized epilepsy,^{40,43,45} and the hippocampus for patients with temporal lobe epilepsy.^{4,6}

DBS for children is often only considered when patients have reached a treatment-refractory stage of their disease, often with few options remaining.³⁰ Most commonly used to treat intractable primary generalized childhood dystonia, the potential for DBS in pediatric populations offers new hope to improve a child's quality of life. Despite its potential value, there remain important unanswered questions regarding DBS for epilepsy in children. Current evidence is limited to case reports and small case series; long-term data regarding its safety and efficacy are lacking. Much of the evidence is translated from adult studies; the procedure and its associated risks as well as device programming and follow-up are modified, thereby posing a challenge to clinicians given the biological differences in children. Although DBS could provide significant seizure freedom for children with DRE, it is not offered routinely, as it is still fairly novel in pediatric populations. The current report is the first to present a synthesis of the available evidence for DBS in children with DRE to assess the efficacy and safety of DBS in pediatric patients with DRE. This systematic review aims to analyze the current literature to understand the effects of DBS for epilepsy in a pediatric population, focusing on safety and efficacy and highlighting patient selection, DBS placement and settings, and seizure freedom.

Methods

Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews

and Meta-Analyses (PRISMA)²⁸ guidelines and recommendations. The strategy was developed a priori but not published. A literature search was performed using MEDLINE, Embase, and Cochrane CENTRAL on November 17, 2017, by a librarian (M.A.). The database searches used keywords (individually and/or in combination), specifically “electrical stimulation,” “deep brain stimulation” or “DBS,” and “seizure(s),” or “epilepsy” with the appropriate subject headings. The reference lists of retrieved review articles were reviewed to identify additional relevant articles.

Study Selection and Data Extraction

Retrieved studies were systematically assessed using inclusion and exclusion criteria by 2 reviewers (H.Y. and E.T.). Inclusion criteria were 1) diagnosis of DRE, as defined by the individual studies; 2) treatment with DBS; 3) inclusion of at least 1 pediatric patient; and 4) patient-specific data. Exclusion criteria for the systematic review included 1) missing data for age, DBS target, or seizure freedom; 2) nonhuman subjects; and 3) editorials, abstracts, review articles, and dissertations. When duplicate studies were found, only the most recent and complete reports were included for quantitative assessment.

All data were extracted from article texts, tables, and figures. Each retrieved article was reviewed by 2 investigators independently (H.Y. and E.T.). Any discrepancies were reviewed in conference.

Results

Literature Search

The search strategy identified a total of 6352 studies (Fig. 1). After removal of 1490 duplicate studies, inclusion and exclusion criteria were applied to the titles of the 4862 articles. This yielded 26 studies that underwent full-text analysis, of which 5 studies did not meet the inclusion criteria (Fig. 1). When patients originated from the same hospital, the demographic information of the patients was analyzed. Six patients were included in multiple papers,^{27,33,40,42,44} and only the most recent publication was included in this analysis. Thus, 21 studies were included.

Cohort Description

A total of 40 patients were included in this systematic review of pediatric epilepsy patients treated with DBS (Table 1). The ages ranged from 4⁴⁰ to 18 years. Sex was not reported for 10 patients.^{40,44} Of the remaining 30 patients, there were 19 males and 11 females. The shortest follow-up duration was 0.5 months,⁴⁴ and this was in the context of a protocol to follow DBS of the hippocampus with a subsequent temporal lobectomy. The majority of patients (n = 24) had at least 18 months of follow-up when seizure freedom was measured, although 2 patients only had reported follow-up of 2 weeks.

Seizure Characteristics

All patients included were offered DBS treatment because their epilepsy was refractory to medical treatment. These patients had a wide range of etiologies ranging from focal epilepsy secondary to focal cortical dysplasia

FIG. 1. PRISMA flowchart. Figure is available in color online only.

to multifocal epilepsy resulting from genetic or syndromic conditions. Two patients were previously diagnosed with tuberous sclerosis,^{3,40} 2 patients had mesial temporal sclerosis,^{7,41} 2 had hypothalamic hamartomas,¹⁸ and 3 had cortical dysplasia.^{2,5,20}

One patient included in the analysis was one of 3 individuals from a family with North Sea progressive myoclonus epilepsy and confirmed *GOSR2* mutation.¹ All 3 members of this family presented with ataxia, tremor, early gait difficulties, and myoclonic and generalized tonic-clonic epilepsy, and each received benefit from DBS treatment; only 1 of these patients was a child. Kokoszka et al.²⁰ presented a patient with West syndrome who, historically as an infant, had classic findings of infantile spasms with the electroencephalogram having shown hypsarrhythmia. Another child had been diagnosed with autosomal-dominant nocturnal frontal lobe epilepsy that did not respond to DBS treatment.⁵ Nine patients from the same study all had Lennox-Gastaut syndrome,⁴⁰ a childhood epilepsy pathology characterized by drug-resistant generalized seizures and cognitive deterioration. These seizures were associated with slow spike-wave complexes and bursts of rapid rhythms during slow sleep on electroencephalography.

Seizure type was described in a heterogeneous manner by the different studies. The majority of patients (n = 27) had generalized or secondarily generalized seizures (Table 2). Four patients had previous episodes of status epilepticus,^{7,24,45} including 1 patient who was in a continu-

ous 4-week episode of intractable status epilepticus, which only improved after DBS treatment.²⁴

Five patients had previous surgery in an attempt to treat their epilepsy.^{2,5,9,20,37} The operations included a biopsy to identify a possible epileptogenic lesion,² a right precentral frontal lobe resection⁵ and a left anterior temporal lobectomy⁹ to attempt seizure reduction, and VNS;³⁷ 1 patient had already undergone right fontal lobectomy, complete corpus callosotomy, VNS, left temporal lobectomy, and posterior quadrantectomy.²⁰ These procedures did not achieve the desired seizure reduction, and DBS was offered as an alternative treatment. Two patients had subacute electrical stimulation of the hippocampal formation or gyrus for 2–3 weeks to identify and suppress temporal lobe epileptogenesis prior to temporal lobectomy.⁴¹ In the 16 days of monitoring, DBS treatment eliminated seizures for one of these patients. Given the complex and dissimilar histories of these patients, it is difficult to correlate specific risk factors that would predict the effectiveness of surgery or DBS.

Since all patients included in this study were diagnosed with DRE, these children were receiving at a minimum 2 seizure medications, and 1 child had been on 6 seizure medications simultaneously prior to DBS surgery.²⁴ Although most of the studies did not report post-DBS medication changes, all studies that reported these data in tables or text demonstrated a decrease in antiepileptic medication.^{3,29,40,45}

TABLE 1. Demographic information

Authors & Year	Country	Pt No.	Sex	Age (yrs)	Notes
Anderson et al., 2017	South Africa	1	M	9	North Sea progressive myoclonus epilepsy w/ <i>GOSR2</i> mutation
Benabid et al., 2002	France	2	F	5	Cortical dysplasia
Benedetti-Isaac et al., 2015	Colombia	3	M	16	Tuberous sclerosis
		4	M	16	Autism
Chabardès et al., 2002	France	5	M	9	Focal cortical dysplasia; infection & temporary unilat battery removal
		6	M	17	
Cukiert et al., 2017 ⁷	Brazil	7	F	14	Lt mesial temp sclerosis, recurrent status epilepticus
Ding et al., 2016	China	8	M	10	Febrile convulsive seizures
Fisher et al., 1992	US	9	M	16	
Khan et al., 2009	UK	10	M	16	Rt hypothalamic hamartoma
		11	F	13	Lt hypothalamic hamartoma
Kim et al., 2017	South Korea	12	F	16	
Kokoszka et al., 2018	US	13	M	14	Type 1 focal cortical dysplasia
Lee et al., 2017	Taiwan	14	F	17	4 wks of status epilepticus prior to DBS
Lee et al., 2006	South Korea	15	M	14	Removal due to infection
		16	F	14	
Lee et al., 2012	South Korea	17	F	14	
		18	M	14	
		19	M	18	
Lim et al., 2007	Taiwan	20	M	18	ATN & STN insertion, removal of STN
Valentín et al., 2013	UK/Spain	21	F	18	
		22	M	14	
Valentín et al., 2017	UK	23	M	9	
		24	F	8	
		25	F	17	
Velasco et al., 1987	Mexico	26	M	15	Previous status epilepticus
		27	M	16	Previous status epilepticus
Velasco et al., 2000 ⁴¹	Mexico	28	F	11	Medial temp sclerosis
		29	M	11	
Velasco et al., 2000 ⁴⁴	Mexico	30		15	
		31		8	
		32		7	Explanted due to skin erosion
		33		9	Explanted due to skin erosion
		34		13	
		35		11	Rupture of electrode lead, replacement
		36		10	
		37		4	Tuberous sclerosis
		38		13	
		39		13	Cerebral infarct
Velasco et al., 2007 ⁴²	Mexico	40	M	14	

Pt = patient; temp = temporal; UK = United Kingdom.

DBS Location and Seizure Freedom

The DBS target was determined largely by the institution and the experience of the surgeon treating adult populations (Table 3). Seizure reduction was heterogeneously reported, mostly by self-report at follow-up appointments; only 1 study⁷ clarified the use of a seizure diary. Ultimately, 5 of the 40 patients (12.5%) had an International League Against Epilepsy class I (i.e., seizure-free) out-

come. Among the 40 patients, 34 (85%) patients had seizure reduction with DBS stimulation, and 6 (15%) patients had no seizure reduction.

There were 18 patients from 7 different studies who had DBS electrodes placed in the CM bilaterally or unilaterally.^{13,19,37,38,40,44,45} There was seizure reduction in 17 of these patients, ranging from 30% to 100%. There were 9 patients with Lennox-Gastaut syndrome who were treated

TABLE 2. Epilepsy characteristics

Authors & Year	Pt No.	Duration of Epilepsy (mos)	Sz Frequency (no./mo)	Localization	Syndrome	Antiepileptic Agents	Other Treatment
Anderson et al., 2017	1	36	6	Generalized	North Sea progressive myoclonus epilepsy	Carbamazepine, sodium valproate	
Benabid et al., 2002	2	36	210	Lt parietal	NA	Phenytoin, carbamazepine, stiripentol, γ -vinyl-GABA, clonazepam; pre-Sx phenobarbital, valproic acid, clonazepam	Previous Lt parietal biopsy
Benedetti-Isaac et al., 2015	3	188	1200	Generalized	NA	Carbamazepine, clonazepam	
	4	132	12	Generalized	NA	Phenytoin, clonazepam, lorazepam	
Chabardès et al., 2002	5	103	245	Rt central	NA	Valproate, lamotrigine	Rt precentral frontal resection
	6	132	600	Lt insulofrontal	ADNFLE	Phenytoin, clonazepam, levetiracetam, piracetam	
Cukiert et al., 2017 ⁷	7	132	10	Lt temp	NA	NA	
Ding et al., 2016	8	126	NA	Generalized	NA	NA	Previous Lt anterior temp lobectomy
Fisher et al., 1992	9	168	30	Generalized	NA	Phenytoin, clonazepam	
	10	96	12	Generalized	NA	Multiple	Refused resective surgery
Khan et al., 2009	11	141	120	Gelastc, generalized	NA	NA	
Kim et al., 2017	12	180	NA	Bilat frontal parietal	NA	NA	
Kokoszka et al., 2018	13	162	NA	Lt temp	West syndrome	NA	Concurrent RNS; previous rt frontal lobectomy, complete corpus callosotomy, VNS, Lt temp lobectomy, & posterior quadrantectomy
	14	60	77	Generalized	NA	Lorazepam, levetiracetam, valproic acid, topiramate, perampanel, midazolam	Ketogenic diet, midazolam infusion
Lee et al., 2017	15	NA	42	Generalized	Global cognitive delay	Topiramate, lamotrigine, valproate, vigabatrin	
Lee et al., 2006	16	NA	450	Rt motor	NA	NA	
	17	36	1200	Generalized	NA	NA	
Lee et al., 2012	18	60	95	Bilat frontal	NA	NA	
	19	84	30	Bilat centroparietal	NA	NA	
Lim et al., 2007	20	174	26	Generalized	NA	Carbamazepine, topiramate, clonazepam	
Valentín et al., 2013	21	168	3006	Generalized	NA	Levetiracetam, lamotrigine, acetazolamide, clonazepam	Previous VNS
Valentín et al., 2017	22	NA	10	Focal motor	NA	NA	
	23	NA	>1000	Generalized	NA	NA	
	24	NA	900	Generalized	Genetic syndrome NYD	NA	

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TABLE 2. Epilepsy characteristics

Authors & Year	Pt No.	Duration of Epilepsy (mos)	Sz Frequency (no./mo)	Localization	Syndrome	Antiepileptic Agents	Other Treatment
Velasco et al., 1987	25		10–37	Generalized	NA	Phenytoin, carbamazepine, valproate	AED overdose
	26		7–150	Generalized	NA	Phenytoin, carbamazepine, clonazepam	AED overdose
	27		26–60	Generalized	NA	Primidone, carbamazepine, clonazepam	
Velasco et al., 2000 ⁴¹	28	72	4	Focal	NA	Oxcarbazepine	Post-DBS temp lobectomy
	29	48	12	Generalized	NA	Carbamazepine, valproate	Post-DBS temp lobectomy
Velasco et al., 2000 ⁴⁴	30	NA	119	Generalized	NA	NA	
Velasco et al., 2006	31	12	3119	Generalized	Lennox-Gastaut	NA	
	32	12	4300	Generalized	Lennox-Gastaut	NA	
	33	24	3780	Generalized	Lennox-Gastaut	NA	
	34	96	3030	Generalized	Lennox-Gastaut	NA	
	35	108	1200	Generalized	Lennox-Gastaut	NA	
	36	115	50	Generalized	Lennox-Gastaut	NA	
	37	46	150	Atypical	Lennox-Gastaut	NA	
	38	108	35	Generalized	Lennox-Gastaut	NA	
	39	72	50	Atypical	Lennox-Gastaut	NA	
Velasco et al., 2007 ⁴²	40	36	25	Generalized		Carbamazepine, phenytoin	

ADNFLE = autosomal-dominant nocturnal frontal lobe epilepsy; AED = antiepileptic drug; NA = not available; NYD = not yet diagnosed; Sx = symptom(s); Sz = seizure.

with unilateral or bilateral CM DBS.⁴⁰ This study included the 5 patients with unilateral CM electrode placement and stimulation, due to inaccurate placement of one of 2 bilateral CM electrodes.

Eight patients from 6 different studies had DBS electrodes placed in the anterior thalamic nucleus (ATN) bilaterally.^{20,24–26,29,38} There was seizure reduction in 6 of the 8 patients, with seizure reduction ranging from 37% to 90%. The 2 patients with no improvement in seizure outcome had seizures localized to the bilateral frontal lobe and bilateral centroparietal lobe.²⁶ The most recent study²⁰ uniquely attempted the use of a right temporal cortical strip for RNS and a left thalamic depth electrode simultaneously inserted during the same operation, using an off-label application of the RNS for children. A corticothalamic stimulation trial showed improved 50% reduction in seizure frequency with DBS and cortical detection compared with unilateral cortical stimulation from RNS alone.

Five patients had DBS electrodes placed in the hippocampus.^{7,9,41,42} Two of these patients with intractable temporal lobe seizures had bilateral depth and subdural electrodes implanted to determine the location and extent of the epileptic focus before a temporal lobectomy.⁴¹ These electrodes only provided stimulation for 16 days, with seizure freedom in one patient and no change in the other. Three of the 5 patients were treated with DBS electrode placement in the hippocampus unilaterally. Two patients

had left hippocampal DBS placement: one patient had left mesial temporal sclerosis with 0% seizure rate reduction,⁷ and the other patient was enrolled in a double-blind study where the stimulation was on or off for 1 month following implantation and demonstrated 64% seizure reduction when the stimulation was on.⁴² The patient with right hippocampal DBS placement had previously undergone left anterior temporal lobectomy, with 80% seizure reduction.

Three patients had bilateral subthalamic nucleus (STN) DBS placement, in an attempt to inhibit the substantia nigra from spreading paroxysmal discharges to disrupt seizure pathways.^{5,25} One of these 3 patients had successful seizure reduction (71.4%) after 1 month, but the case was complicated by infection of the implantable pulse generator and the entire system had to be explanted.²⁵ Similarly, another patient with focal cortical dysplasia had bilateral STN placement after a failed precentral frontal resection also had an implantable pulse generator infection with a temporary explantation; during this period, the seizure frequency increased.⁵ A third patient who was diagnosed with autosomal-dominant nocturnal frontal lobe epilepsy was treated with bilateral STN DBS placement and had no change in seizure frequency.⁵ One child in whom a previous left parietal biopsy had led to the diagnosis of cortical dysplasia underwent left-sided STN placement, with an 80.7% seizure reduction.² One patient initially underwent insertion of ATN and STN electrodes, but the STN

TABLE 3. DBS and seizure outcomes

Authors & Year	Pt No.	DBS Location	Anesthesia	Frequency (Hz)	Pulse Width (μsec)	Volt/Current	Sz Reduction	FU (mos)	Notes
Anderson et al., 2017	1	Bilat cZI	NR	130	450	2.1 mA	100% of GTC	84	
Benabid et al., 2002	2	Lt STN	GA	130	90	5.2 V	80.7%	30	
Benedetti-Isaac et al., 2015	3	Bilat pHyp	GA	185	90	2.7 V	100%	48	Improved aggression
	4	Bilat pHyp	GA	185	90	2.8 V	89.6%	2	Aggression improved for only 2 mos
Chabardès et al., 2002	5	Bilat STN	GA	130	90	3.8 V	67.8%	15	
	6	Bilat STN	GA	130	60	3.0 V	0%	6	
Cukiert et al., 2017 ⁷	7	Lt hippo-campus	GA	130	300	2.0 V	0%	>6	
Ding et al., 2016	8	Rt hippo-campus	GA	130	300	2.2 V	80%	18	
Fisher et al., 1992	9	Bilat CM	NR	65	90	0.5–10 V	~30%	>3	50% reduction stimulator off, 15% reduction w/ stimulator on
Khan et al., 2009	10	Rt MMT	GA	140	90	3 V	100%	21	
	11	Lt MMT	GA	140	90	3.5 V	86%	13	Returned to school after 2 yrs
Kim et al., 2017	12	Bilat CM	GA	130	90	1.5–2.0 V	92.9%	18	
Kokoszka et al., 2018	13	Bilat ATN	NR	100; 200	160; 160	0.5 mA	80–90%	19	Responsive neurostimulation also used
Lee et al., 2017	14	Bilat ATN	NR	145	120	8 V	90%	1.5	
Lee et al., 2006	15	Bilat STN	Local	130	90	NA	71.4%	1	
	16	Bilat ATN	Local	130	90	NA	50%	2	
Lee et al., 2012	17	Bilat ATN	Local	100–185	90–150	1.5–3.1 V	80.8%	59	
	18	Bilat ATN	Local	100–185	90–150	1.5–3.1 V	0%	24	
	19	Bilat ATN	Local	100–185	90–150	1.5–3.1 V	0%	28	
Lim et al., 2007	20	Bilat ATN	Local	180	90	6 V	37%	48	
Valentín et al., 2013	21	Bilat CM	GA	60	90	5 V	50% for complex partial; 95% for simple partial	36	
Valentín et al., 2017	22	Bilat ATN	GA	NA	NA	NA	>60%	12	
	23	Bilat CM	GA	NA	NA	NA	>60%	48	
	24	Bilat CM	GA	NA	NA	NA	0%	18	
Velasco et al., 1987	25	Bilat CM	NR	60–100	100	2.0 mA	85% for tonic-clonic; 100% for complex partial	3	Reduced AED dosages & side effects
	26	Bilat CM	NR	60–100	100	2.0 mA	100% for tonic-clonic, complex partial	3	Reduced AED dosages & side effects
	27	Bilat CM	NR	60–100	100	2.0 mA	95% for tonic-clonic; 100% for complex partial	3	
Velasco et al., 2000 ⁴¹	28	Bilat hippo-campus	NR	130	450	2–4 mA	0%	0.5	
	29	Bilat hippo-campus	NR	130	450	2–4 mA	100%	0.5	
Velasco et al., 2000 ⁴⁴	30	Bilat CM	GA	60	NA	4–6 V	80.60%	>12	
Velasco et al., 2006	31	Lt CM	GA	130	450	6–8 V	100%	18	
	32	Bilat CM	GA	130	450	6–8 V	100%	18	
	33	Rt CM	GA	130	450	6–8 V	95%	18	
	34	Bilat CM	GA	130	450	6–8 V	95%	18	
	35	Bilat CM	GA	130	450	6–8 V	95%	18	

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TABLE 3. DBS and seizure outcomes

Authors & Year	Pt No.	DBS Location	Anesthesia	Frequency (Hz)	Pulse Width (μsec)	Volt/Current	Sz Reduction	FU (mos)	Notes
Velasco et al., 2006 (continued)	36	Bilat CM	GA	130	450	6–8 V	70%	18	
	37	Rt CM	GA	130	450	6–8 V	58%	18	
	38	Rt CM	GA	130	450	6–8 V	53%	18	
	39	Lt CM	GA	130	450	6–8 V	30%	18	
Velasco et al., 2007 ⁴²	40	Lt hippo-campus	NR	130	450	3.0 mA	64%	18	

cZI = caudal zona incerta; FU = follow-up; GA = general anesthesia; GTC = generalized tonic-clonic; MMT = mamillothalamic tract; NR = not reported; pHyp = posteromedial hypothalamus; Volt = voltage.

electrode was explanted after the ATN electrode proved to provide better seizure relief.²⁹

Two patients underwent bilateral posteromedial hypothalamus DBS in an attempt to treat both epilepsy and aggression.³ Both patients had improved seizure control, with 89.6% and 100% seizure frequency reduction. The aggression for both patients also improved, although the improvement in 1 patient was only temporary for 2 months.

Two patients with hypothalamic hamartomas were treated with unilateral mamillothalamic tract DBS; both patients had favorable results with seizure reduction of 86% and 100%.¹⁸

Finally, 1 patient with North Sea progressive myoclonus epilepsy underwent bilateral caudal zona incerta DBS placement and showed 100% reduction in seizures at 84 months.¹ This treatment was also effective for 2 adult relatives with the same pathology due to genetic mutation of *GOSR2*.

Complications

The majority of studies noted very few or no complications, and there were no deaths. There were 4 complications, all due to infection. One patient required an explant of the DBS due to infection of the anterior chest battery with *Staphylococcus aureus*.²⁵ There were also 2 occurrences of skin erosion of batteries in children 7 and 9 years old, leading to explantation.⁴⁰ The second child retained the seizure freedom after DBS explantation. Finally, 1 patient had electrode lead breakage after 31 months, and the battery and electrodes were replaced, with the same favorable seizure outcome.⁴⁰

Discussion

In this systematic review of pediatric cases of epilepsy treated with DBS, 40 patients with DRE from 21 papers were analyzed. There were 18 patients with bilateral or unilateral CM electrodes,^{13,19,37,38,40,44,45} 8 patients with bilateral ATN electrodes,^{20,24–26,29,38} 3 patients with unilateral hippocampal electrodes,^{7,9,42} 2 patients with bilateral hippocampal electrodes,⁴¹ 3 patients with bilateral^{5,25} and 1 patient with unilateral STN electrodes,² 2 patients with bilateral posteromedial hypothalamus electrodes,³ 2 patients with unilateral mamillothalamic tract electrodes,¹⁸ and 1 patient with caudal zona incerta electrode placement.¹

In summary, 34 of the 40 (85%) patients had reduction in seizure frequency with DBS stimulation.

Only 6 patients demonstrated no reduction in seizure frequency.^{5,7,26,38,41} Two of these patients had bilateral ATN placement for seizures identified in the bilateral frontal hemispheres and bilateral centroparietal lobes.²⁶ A patient with autosomal-dominant nocturnal frontal lobe epilepsy who showed seizures originating from the left insulofrontal cortex did not have any seizure improvement with bilateral STN DBS.⁵ Another nonresponder was an 8-year-old girl with a genetic syndrome of unknown etiology.³⁸ Her bilateral CM DBS treatment was unsuccessful at 12 months with a slight worsening of seizure frequency, and thus the DBS electrodes were removed at 18 months. The patient with bilateral hippocampal DBS placement prior to temporal lobectomy who demonstrated no response was the only participant without a positive response to treatment in the study.⁴¹ This may have been because this patient had stimulation contacts located in the white matter adjacent to the hippocampus instead of the hippocampus proper. The last nonresponder was the only nonresponder in a prospective, controlled, randomized, double-blind study looking at hippocampal DBS in refractory temporal lobe epilepsy.⁷ This 14-year-old girl with left mesial temporal sclerosis demonstrated no change in her simple partial seizures and an increase in her complex partial seizures after left hippocampal DBS.

In this cohort, 16 patients^{40–42,44,45} were from Mexico, 13 of whom had DBS placement in the CM. The earliest study was from 1987⁴⁵ and drew on the hypothesis that the red nucleus, and the CM situated above it, can induce cortical desynchronization and block epileptic synchronous discharges. Since the SANTE trial demonstrated 38% seizure reduction compared with 14.5% in a multicenter, randomized, double-blinded parallel-group study, the ATN has become the most effective and acceptable therapy for refractory epilepsy.^{13,35} Although DRE is heterogeneous in clinical presentation, certain brain networks may be more important for cortical synchronization and seizure propagation, thus making nodes of these networks more important neuromodulation targets in epilepsy. For example, the cortico-striato-thalamic network and the limbic circuit of Papez have been postulated as targets for stimulation.^{23,34} One hypothesis for the mechanism of ATN DBS is the modulation of ipsilateral Papez structures such as the en-

torhinal cortex, hippocampus, parahippocampal gyrus, mammillothalamic tract, cingulate, and inferior temporal gyrus.^{15,23,39}

Even in children, DBS is now used in conjunction with other treatments. Kokoszka et al.²⁰ used RNS as an adjunct to DBS, providing a reversible and modulatory treatment option that provides a capacity for chronic recording of brain activity to better localize seizure foci. Their treatment in a nonambulatory, nonverbal 14-year-old boy not only decreased seizure frequency and severity, but also improved his behavior, attentiveness, and level of engagement at school. This boy's seizures did not respond to antiepileptic medications, right frontal lobectomy, complete corpus callosotomy, VNS, left temporal lobectomy, or posterior quadrantectomy. At 19 months' follow-up, cortical stimulation resulted in sustained reduction in both seizure frequency and severity and subsequent DBS reduced seizure frequency by another 50%. This paper is not a direct comparison between DBS and RNS, as the patient in whom both modalities were used had a complex resection history and possibly unique neural circuitry. Velasco et al.⁴¹ also utilized hippocampal DBS as an adjunct to temporal lobectomy. Taking patients completely off antiepileptics, in correctly placed hippocampal DBS electrodes, continuous high-frequency and low-intensity stimulation of the anterior pes hippocampi and parahippocampal gyrus close to the amygdaloid nucleus and entorhinal cortex increases seizure threshold and decreases clinical seizures. They also conducted a histopathological study following the temporal lobectomy, showing no difference between the stimulated or nonstimulated hippocampus, suggesting that the DBS mechanisms affect physiology independent of tissue pathology.

The specific indications for DBS for the treatment of childhood epilepsy have yet to be defined. It is often trialed after failed ablative surgery if there is too much risk for resective surgery or the target for resective surgery is unclear. There are no studies that have compared DBS to other neuromodulatory systems, such as RNS or VNS.

Given that the majority of studies included both adult and pediatric patients, the complications specific to children were not thoroughly analyzed and synthesized in this paper. In this series, there were 4 patients who required permanent or temporary explantation due to infection or skin erosion.^{5,25,40} One patient required DBS electrode replacement after a lead was broken.⁴⁰ The youngest patient in this cohort was 4 years old, and it is currently unreported if younger children would benefit from DBS for DRE. The long-term complications of DBS in children is not yet understood, although one may hypothesize of unknown migration challenges with placing a DBS electrode in a growing brain.

Limitations of this study include the inclusion of only 1 randomized control trial,⁷ 5 blinded studies,^{13,29,37,42,44} and 8 prospective trials,^{9,13,19,26,29,37,40–42,44} with the remaining 12 studies being retrospective case reports and case series. Furthermore, it is difficult to analyze and compare the effectiveness of DBS between studies, as different metrics and outcomes are reported. The majority of studies determined seizure frequency by patient or caregiver report at clinical follow-up instead of specifying the use of a seizure

diary or electroencephalography. The characterization of clinical presentation and etiology of seizures are reported in a heterogeneous manner. The rate of seizure frequency was usually measured at the last follow-up, but this ranged anywhere from 16 days to 84 months. Furthermore, there was an inconsistent presentation of antiepileptic medication at the time of treatment and whether there was a reduction or freedom from seizure medication after DBS treatment.

Conclusions

This is the first systematic review that analyzes the effectiveness of DBS on epilepsy in children and youth. Overall, the outcomes analyzed suggest promise for bilateral DBS stimulation of the ATN or CM to achieve a reduction in seizure frequency. Given the initial nascent results seen in a few patients with DBS placement in the hippocampus, STN, posteromedial hypothalamus, mammillothalamic tract, or caudal zona incerta, further understanding of the pathways may better direct the use of these anatomical targets for specifically indicated epilepsy patients. Future studies directed at blinded randomized control trials of stimulation-on/-off states of DBS after placement, with a consistent framework for the reporting of outcomes and complications, will lead to a better understanding of the best clinical scenarios to utilize DBS in children with epilepsy. This would provide an adjunct treatment option for children with DRE who are not candidates for resective surgery.

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Reviewed submitted version of manuscript: Yan, Anderson, Abel, Donner, Kalia, Drake, Rutka, Ibrahim. Approved the final version of the manuscript on behalf of all authors: Yan. Study supervision: Ibrahim.

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