NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of deep brain stimulation for refractory epilepsy in adults

Epilepsy causes seizures because of abnormal electrical activity in the brain. If it cannot be controlled by drugs it is called refractory epilepsy. In this procedure, electrodes are placed deep into the brain. They are connected by wires to a small electrical stimulator implanted under the skin on the chest. The wires pass under the skin behind the ear and down the neck. The aim is that electrical stimulation will stop abnormal electrical activity in the brain and reduce seizures.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in October 2019 and updated in January 2020.

Procedure name

- Deep brain stimulation for refractory epilepsy in adults

Professional societies

- Society of British Neurological Surgeons
- Association of British Neurologists
- Royal College of Surgeons of England
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow

Description of the procedure

Indications and current treatment

Epilepsy is a neurological condition characterised by episodes of abnormal electrical activity in the brain (recurrent seizures). The seizures can be focal or generalised. The main treatment for epilepsy is anti-epileptic drugs taken to prevent or reduce the occurrence of seizures. However, many people have drug-resistant (refractory) epilepsy (estimates vary between 20% and 40% of people with epilepsy). They experience frequent seizures and are at risk of status epilepticus and sudden unexpected death in epilepsy. Surgery may be considered for refractory epilepsy. Surgical options include open surgical resection (such as lesionectomy, anterior temporal lobectomy or hemispherectomy) or disconnection (such as multiple subpial transection or

corpus callosotomy), neuroablation (using stereotactic radiosurgery, radiofrequency thermocoagulation or MRI-guided focused ultrasound) or neuromodulation (such as cranial nerve stimulation, deep brain stimulation or closed loop stimulation).

What the procedure involves

Deep brain stimulation involves implanting electrodes into specific target areas of the brain. Although the mechanisms of action are not fully understood, the aim of the procedure is to reduce or suppress seizure frequency. A potential advantage of the procedure is its reversibility. It is an option for some patients with medically refractory epilepsy when resective surgery is not indicated.

Deep brain stimulation for epilepsy is done using general or local anaesthesia. A stereotactic frame may be used. Imaging (MRI or CT) is used to identify the target area of the brain (most commonly the anterior nucleus of the thalamus but may include the centromedian thalamic nucleus, hippocampus and nucleus accumbens). One or more small holes are drilled in the skull and electrodes are implanted into the target area. The electrodes are connected to an implantable neurostimulator by means of leads that are tunnelled under the skin of the neck and scalp. The neurostimulator is surgically placed into a subcutaneous pocket below the clavicle. Postoperative imaging is usually used to confirm the location of the electrodes. A handheld remote-control programming unit is used to turn the neurostimulator on or off, adjust stimulation parameters, and monitor activity.

Efficacy summary

Seizure frequency

An RCT of 109 patients who had anterior thalamic DBS for refractory epilepsy reported a 29% greater reduction in seizures for 54 patients with stimulation ‘on’ compared with 55 patients with stimulation ‘off’ (control) at the end of a 3-month blinded phase (p=0.002)[1]. Unadjusted reductions in seizure frequency were 15% in the control group and 40% in the stimulated group. After the blinded phase, all patients received stimulation and there was a 56% median reduction in seizure frequency at 2-year follow-up (n=81). In total, 14 patients were seizure free for at least 6 months, 8 for at least 1 year, 4 for at least 2 years and 1 for over 4 years[1]. In 59 patients who were followed up to 5 years, there was 69% median reduction in seizure frequency from baseline (p<0.001)[2].

An RCT of 18 patients with focal, refractory epilepsy, who had DBS of bilateral anterior nucleus thalamus, reported 23% reduction of total seizure frequency from baseline in stimulation ‘on’ group (n=8, p=0.048), and no reduction in stimulation ‘off’ group (n=10, p=0.85) at the end of 6 months blinded phase. After

blinded phase, all patients received stimulation. When comparing 6 months of stimulation with baseline for all patients(n=17), there was 22% reduction in the frequency of seizures (p=0.009)[3].

In an RCT of 16 patients who had hippocampal DBS for refractory temporal lobe epilepsy, 88% (7/8) of active group and 38% (3/8) of control group had ≥50% seizure frequency reduction during the 6-month blinded phase. 50% (4/8) of the active group were seizure-free at 6-month follow-up[4].

In a systematic review and meta-analysis of 61 patients who underwent DBS for refractory temporal lobe epilepsy, the pooled seizure reduction rate with at least 70% of seizure frequency reduction was 59% (95% CI, 45-72%)[5].

A Cochrane review of 7 studies, which included 45 patients (excluding cortical stimulation, responsive neuro stimulation and SANTE trial) reported subgroup analysis for different DBS targets. For centromedian thalamic nucleus stimulation (n=6, 12 treatment periods), there was a non-significant 7% (95% CI, -44.1 to 58.2, p=0.79) seizure frequency increase during stimulation 'on' compared to stimulation 'off' periods. In Hippocampal stimulation (n=15), there was significantly reduced seizure frequency in active stimulation compared to sham stimulation, with pooled mean difference of -28% (95%CI, -34.1 to -22.2, p<0.00001). In nucleus accumbens stimulation (n=4, 8 treatment periods), there was non-significant -34% (95%CI, -117.4 to 49.8, p=0.43) lower seizure frequency compared to sham stimulation. Results for seizure freedom and responder rate (>50% seizure reduction) were not significant between active and sham stimulation in all the three DBS targets[6].

In a systematic review of 40 patients who are children with refractory epilepsy, 85% (34/40) of patients had seizure reduction from all DBS targets. 12.5% (5/40) were seizure free. Overall mean seizure frequency reduction from baseline was 66% (range, 0 to 100 %) from all DBS targets[7].

In a non-randomized comparative study of 11 patients (6 generalised epilepsy and 5 frontal epilepsy) who underwent bilateral centromedian thalamic nucleus stimulation, the percentage of responders with ≥50% seizure reduction was 100% (6/6) for generalised epilepsy, and 20% (1/5) for frontal epilepsy at 6 months, 83% (5/6) for generalised epilepsy and 0% (0/4) for frontal epilepsy at 12 months follow-up. In the long-term extension phase of generalised epilepsy (follow-up range 20 to 72 months), 83% (5/6) showed ≥50% reduction in seizure frequency, including 3 seizure free. In the long-term extension phase of frontal epilepsy (follow-up range 22 to 48 months), 50% (2/4) (patients had ≥50% reduction in seizure frequency[8].

In a case series of 29 patients with refractory epilepsy who underwent anterior thalamic DBS, there was a median seizure frequency reduction of 70% at 1 year

(n=29), 74% at 2 years (n=26), 78% at 3 years (n=24), 71% at 5 years (n=20), 68% at 7 years (n=12), 67% at 9 years (n=10) and 67% at 11 years (n=2) follow-up ($p<0.001$ for all years). 24.1% (7/29) were seizure-free for at least 6 months and 14% (4/29) were seizure-free for at least 12 months during the 11-year follow-up[9].

Quality of life

The RCT of 109 patients reported that the Quality of Life in Epilepsy (QOLIE-31) score was statistically significantly improved after 13 and 25 months follow-up (n= 102 and 98, respectively; $p < 0.001$; all patients received stimulation after an initial 3-month blinded phase)[1]. In 80 patients who were followed up to 5 years, QOLIE-31 score continued to improve significantly ($p<0.001$)[2]. The trial also found that proportion of participants with injuries resulting from seizures were significantly reduced by DBS over 3 months (7% with DBS vs. 26% with control; $p=0.01$)[1].

In the Cochrane review 7 studies which included 45 patients, there was no significant different in quality of life scores between active and sham stimulation in both hippocampal stimulation (n=3, 6 treatment periods) and nucleus accumbens stimulation (n=4, 8 treatment periods) ($p=0.84$ and 0.59 respectively)[6].

In the non-randomized comparative study of 11 patients reported an improvement in median Quality of Life in Epilepsy score from 53.9 at pre-DBS to 68.8 at 6 months post-DBS (n=7, $p=0.018$)[8].

Safety summary

Haemorrhage

The RCT of 109 patients implanted with DBS electrodes reported that 5% (5/109) of patients had asymptomatic haemorrhages detected incidentally by neuroimaging[1].

The Cochrane review of 45 patients with DBS for refractory epilepsy reported that 1 patient had asymptomatic minimal haemorrhage on post-operative CT[6].

In the case series of 29 patients who underwent anterior thalamic DBS for refractory epilepsy, 1 patient had intracranial haemorrhage causing hemiparesis immediately after DBS lead insertion. The weakness resolved after 3 months of physical therapy[9].

Infection and skin erosions

The RCT of 109 patients implanted with DBS electrodes reported that 13% (14/109) of patients developed implant site infections, either in the stimulator pocket, the tunnelled lead extension tract or at the site of the burr hole. Another patient had a meningeal reaction. All infections were treated with antibiotics, and 9 patients had additional removal of hardware; 3 patients later had reimplantation[1].

THE RCT of 16 patients with hippocampal DBS for temporal lobe epilepsy reported that 13% (2/16) of patients had local erosions at the cranial site of the implant. They were treated with antibiotics[4].

The Cochrane review of 45 patients with DBS for refractory epilepsy reported that skin erosions occurred in 23% (3/13) of patients with centromedian thalamic nucleus stimulation, all requiring explanation. In one study of 9 patients with DBS for hippocampal stimulation, 33% (3/9) of patients had skin erosions and local infection 24 months after implantation, requiring explanation. There was 1 case of local subcutaneous infection from the nucleus accumbens stimulation study (n=4)[6].

In the systematic review of 40 patients who are children with refractory epilepsy, 1 patient had infection at the anterior of the chest, requiring device explanation. 10% (2/40) of patients had skin erosions, requiring explanation[7].

In the case series of 29 patients who had anterior thalamic DBS, 1 patient had superficial infection in the wound site of the chest requiring short-term antibiotics. There was also 1 patient from initial recruitment who developed post-operative deep infection, requiring device removal and intravenous antibiotics. The patient was excluded from the study[9].

In a non-randomized comparative study of 11 patients, 1 patient had device removed 6 months after implantation due to infection[8].

Depression/Suicidal ideation

The RCT of 109 patients reported depression in 15% (8/54) of patients who had DBS (stimulation ‘on’) compared with 2% (1/55) of control patients (stimulation ‘off’) during the blinded phase (p=0.016)[1]. Depression symptoms resolved in 4 of the 8 DBS patients within an average of 76 days (3 patients were on medication for depression at baseline)[1]. In the long-term follow-up study of the same trial reported depression events in 37% (41/110) of total DBS implanted patients at some time after the implant. 66% of the patients who reported depression had history of depression. 1 patient died by suicide, which was not judged to device-related[2].

An RCT of 18 patients with anterior thalamic DBS for focal refractory epilepsy reported 2 cases of transient depression and 1 case of having suicidal thoughts[3]. The Cochrane review of 45 patients with DBS for refractory epilepsy reported only 1 case of depressive mood during the sham stimulation period[6].

In the case series of 29 patients who had anterior thalamic DBS, 17% (5/29) reported depression. 60% (3/5) had history of depression. 7% (2/29) reported suicidal ideation and 1 separate patient committed suicide approximately 7.5 years after implantation, which was not judged as device-related by the investigator[9].

Memory impairment and Neuropsychological outcomes

In the RCT of 109 patients, memory impairment was reported in 13% (7/54) of patients in the DBS group and 2% (1/55) of patients in the control group (p = 0.032) during the blinded phase. No memory impairment was judged to be serious and all resolved over 12–476 days[1]. In the long-term follow-up study of the same trial, memory impairment was reported in 27% (30/110) of total DBS implanted patients at some time after the implant, 50% of them had history of memory impairment[2].

An RCT of 18 patients with anterior thalamic DBS for focal refractory epilepsy reported 17% (3/18) of patients with memory deficit during the 12 months follow-up[3]. In the case series of 29 patients who had anterior thalamic DBS, 24.1% (7/29) reported subjective memory impairment at some time during the follow-up period. 5 patients completed neuropsychological testing and only 1 had a confirmed change from baseline[9].

In the case series of 29 patients, the neuropsychological assessments after more than 1 year of DBS implantation showed significant improvement in immediate verbal memory (p=0.04), delayed verbal memory (p=0.004), full memory quotient(p=0.01) and word fluency test (letter and category, p= 0.01 for both). There were no significant changes in general abilities (IQ, MMSE), information processing or executive function (n=7)[9].

In the Cochrane review of 45 patients, neuropsychological test results were not significant between baseline and stimulation ‘on’ and ‘off’ periods, except 1 patient from hippocampal stimulation study who had worse verbal and visuospatial memory scores when stimulated (values not provided), despite reported subjective memory improvement during the same period[6].

In a 5-year follow-up study of RCT of 109 patients with ANT-DBS, the neuropsychological test composite scores showed significant improvement from baseline to 5 years (n=76) in attention (p<0.001), executive functions (p<0.001), depression (p=0.039), tension/anxiety (p=0.027), total mood disturbance

(p=0.0016), and subjective cognitive function (p<0.001). Other scores such as verbal memory, visual memory, expressive language, and confusion were reported as statistically not significant[2]. In 67 patients who were followed up to 7 years, there was no significant cognitive declines, neurobehavioral problems, subjective cognitive declines, or affective distress (depressive and anxious symptoms). The neuropsychological test scores at 7 years compared to baseline showed significant improvement for visual recall (p=0.01), design fluency(p<0.001), Trailmaking(number-letter switching)(p=0.02), Inhibition/Switching (p=0.02), the Tower task(problem solving) (p<0.001), and simple visual attention (trailmaking number sequencing and letter sequencing , p<0.001 for both)[10].

Status epilepticus

The RCT of 109 patients reported 5% (5/109) of patients had status epilepticus (3 were in the stimulated group during the blinded phase and 2 were after the blinded phase); 2 were identified before initiation of stimulation (in patients who had missed 1 or more doses of their AEDs), 1 was during month 2 of the blinded phase, 1 occurred when the stimulator was turned on after the blinded phase and 1 occurred at month 49, 1 year after stimulation was discontinued[1]. The long-term follow-up study reported total 7 patients (6.4%) had status epilepticus during the study[2].

Anterior thalamic stimulation induced relapsing encephalitis

Anterior thalamic deep brain stimulation induced relapsing encephalitis was reported in a case report of 1 patient who had history of herpes meningoencephalitis at the age of 7 months. The patient's stimulation was turned on 1 month of after the operation and the patient presented to emergency unit with confusion, hallucination, mild apraxia, headache, retrograde amnesia and fever. MRI showed a left temporal-mesial hypersignal. Microbiology test was positive for herpes simplex virus type 1 (HSV-1) confirming the diagnosis of Herpes simplex encephalitis. Patient's clinical conditions improved with anti-viral medication. Seizure disappeared even after the stimulation had been stopped for 4 months, then returned as before[11].

Cerebrospinal fluid (CSF) egress from the DBS electrode

A case of CSF egress from the DBS electrode was reported in case report of 1 patient with anterior thalamic DBS for refractory epilepsy. The patient, who had DBS for 5 years, presented with increasing seizure frequency and a shortened battery longevity within 2 years. MRI showed left sided DBS lead was in the third ventricle leaning on the medial wall of ANT. Electrode revision was performed. Upon disconnecting the proximal lead from the extension connection, cerebrospinal fluid egress through fine gaps between the metallic electrode

contacts and electrode spacing was observed. The patient eventually had centromedian nucleus DBS insertion[12].

Twiddler's syndrome

A case report of 1 patient with anterior thalamic DBS for refractory epilepsy reported twiddler's syndrome, which is the conscious or unconscious manipulation of implantable pulse generators (IPGs). The patient presented with recurrent seizures from failure of her DBS stimulator, 6 months after implantation. Radiographic imaging showed the Implantable Pulse Generators (IPG) had been twisted upon itself causing coiling and looping of extension wires. The patient denied any conscious manipulation of the system. Surgical revision was performed, and the desired stimulation effect was achieved. However, patient developed infection at the extension site, the device was removed at fourth month[13].

Persistent psychiatric side effects following discontinuation of DBS

A case of persistent psychiatric side effects following discontinuation of DBS was reported in a case report. The patient had had focal seizures since age 17. After implantation and stimulation initiation, the patient developed psychiatric side effects (PSEs) of irritability, hostility, aggressiveness, and paranoia. The seizures did not to respond to VNS stimulation. The stimulation was discontinued and the PSEs were treated with medications. But the patient did not return to her pre-implantation state as documented by repeated psychiatric reports and hospitalisations over the next 7 years[14].

Other

The long-term follow-up study of the RCT of 109 patients reported a total of 7 deaths during the 5 years follow-up; 1 patient died before implantation of electrodes because of probable SUDEP, 2 further patients died from SUDEP (1 in the unblinded phase and the other during the long-term follow-up), 1 patient drowned during the long-term follow-up phase, 1 committed suicide, 1 death due to cardiorespiratory arrest and 1 death due to liver cancer. None of the deaths were judged to be device-related[2].

In the case series of 29 patients, there were 4 deaths reported during the 11 years follow-up period. 1 patient died of probable SUDEP 5 years after DBS implantation. 1 patient committed suicide, 1 died from cardiorespiratory arrest from septic shock from non-neurological cause and 1 died from severe intracranial haemorrhage from a traffic accident[9].

In the case series of 29 patients, 6.9% (2/29) had lead fractures, requiring replacement[9]. In the RCT of 109 patients, 5.5% had extension fractures[2]. 1

patient from the systematic review of 40 patients required battery and electrodes replacement due to electrode lead breakage after 34 months[7].

In the RCT of 18 patients, 1 patient experienced twitches in the right side of his face and neck when stimulation was on. The left electrode was explanted and reinserted as the internal capsule was affected. 1 patient developed dysarthria and left cranial nerve palsy 3 days after implantation. She experienced total remission the following week and repeated CT and MRI were normal. 1 patient experienced cerebral stroke 4 months after implantation. This was considered to be unrelated to the operation, but due to his condition of general health. 1 patient had a recurrence of generalised tonic-clonic seizures when her DBS was turned on at 6 months[3].

In the non-randomized comparative study of 11 patients, 1 patient developed transitory agraphia 4 days after implantation, which resolved later[8].

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, professional experts did not list any additional anecdotal adverse events. They considered that the following were additional theoretical adverse events: stroke, pneumothorax and breathing/heart problems.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to Deep brain stimulation for refractory epilepsy in adults. The following databases were searched, covering the period from their start to 23.01.2020: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with refractory epilepsy
Intervention/test	Deep brain stimulation
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 333 patients from 3 RCTs (one of which resulted in 3 publications), 3 systematic reviews, 1 non-randomised comparative study, 1 case series and 4 case reports[1-14].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on deep brain stimulation for refractory epilepsy in adults

Study 1 Fisher R (2010)

Details

Study type	Randomised controlled trial (SANTE)
Country	USA
Recruitment period	Not reported
Study population and number	**n=109(54 DBS Vs 55 Control)** Epileptic patients with medically refractory partial seizures, including secondarily generalized seizures
Age and sex	Mean age: 36 years Sex: 50% (54/109) female
Patient selection criteria	Inclusion criteria: age 18–65 years; partial seizures including secondarily generalised seizures, at least 6 per month, but no more than 10 per day, as recorded in a 3-month daily seizure diary; at least 3 AEDs must have failed to produce adequate seizure control prior to baseline, with 1–4 AEDs used at the time of study entry. Exclusion criteria: progressive neurologic or medical diseases, nonepileptic seizures, IQ < 70, inability to take neuropsychological tests or complete seizure diaries, pregnancy.
Technique	Implantation was with Medtronic DBS leads. Electrodes were implanted in the anterior nucleus of the thalamus (ANT) bilaterally using a stereotactic technique. Stimulation was initially set at 5 V, using 90 microsecond pulses, 145 pulses/second, 1 minute on and 5 minutes off.
Follow-up	**Mean follow-up: not reported (mean duration of active stimulation = 3 years)**
Conflict of interest/source of funding	The study was supported by Medtronic Inc.

Analysis

Follow-up issues: One control group patient had only 66 of 70 protocol-required diary days for the primary analysis and was excluded. An additional patient underwent electrode implantation but was not randomised.

Study design issues:

- Prospective, randomised, double-blind, parallel group design.
- Primary efficacy outcome was reduction in monthly seizure rate from baseline.
- All patients had DBS electrodes implanted.
- One month after implantation, patients were randomised to stimulation at 5 V or no stimulation at 0 V (controls).
- Randomisation was done by a central statistical site, using random numbers tables.
- No care or assessment personnel knew the voltage settings.
- After 3 months of blinded treatment, all patients received stimulation from month 4 to month 13 in an unblinded phase.
- Medications were kept constant during the 3-month blinded phase and the 9-month unblinded phase.
- At the end of month 13, AEDs and stimulation parameters could vary freely.
- A sample size of 102 provided 80% power to detect a 25% larger seizure reduction in the stimulated group.
- Analysis was done using a protocol-prespecified GEE model for repeated measures. The prespecified factors included the intercept, treatment effect, log of the baseline seizure counts, baseline covariates, visit and treatment-by-visit interaction.

Study population issues: The 2 groups were comparable with regard to demographic and seizure history characteristics. 49 patients had previously been treated by vagus nerve stimulation and 27 patients had a history of previous epilepsy surgery.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **108 (54 vs 54)**

Unadjusted median percentage change in seizure frequency from baseline

	DBS	Control
1 month post-implantation (no active stimulation)	-21.3%	-22.2%
Month 1–2	-33.9%	-25.3%
Month 2–3	-42.1%	-28.7%
Month 3–4	-40.4%	-14.5%

GEE model adjusted mean percentage difference in seizure frequency

	Adjusted % difference	p value
Per protocol (54 DBS vs 54 control)		
Month 1–2	20%	0.50
Month 2–3	-10%	0.40
Month 3–4	-29%	0.002
With outlier excluded* (53 DBS vs 54 control)		
Month 1–2	-10%	0.37
Month 2–3	-11%	0.34
Month 3–4	-29%	0.002
Intent-to-treat (54 DBS vs 55 control)		
Month 1–2	19%	0.52
Month 2–3	-10%	0.40
Month 3–4	-29%	0.002
Intent-to-treat with outlier excluded* (53 DBS vs 55 control)		
Month 1–2	-11%	0.34
Month 2–3	-11%	0.34
Month 3–4	-29%	0.002

*One patient had 210 brief partial seizures in the 3 days after initial activation. The stimulator was turned off and the new seizures stopped. Stimulation was later restored with voltage reduced to 4 V.

Improvement in complex partial seizures during blinded phase (outlier removed):
- DBS = 36.3%
- Control = 12.1%, p = 0.04

Injuries produced by seizures during blinded phase:
- DBS = 7%
- Control = 26%, p = 0.01

Median seizure reduction in patients with seizure origin in 1 or both temporal regions:
- DBS = 44.2% (n = 33)
- Control = 21.8% (n = 29), p = 0.025

Safety

Adverse events
808 adverse events were reported in 109 patients between implantation and 13-month follow-up; 238 were considered to be device-related.

Adverse events during the blinded phase:

	DBS	control	p
Depression	14.8% (8/54)	1.8% (1/55)	0.016
Memory impairment	13.0% (7/54)	1.8% (1/55)	0.032
Confusional state	7.4% (4/54)	0% (0/55)	0.057
Anxiety	9.3% (5/54)	1.8% (1/55)	0.113
Paraesthesia	9.3% (5/54)	3.6% (2/55)	0.271
Partial seizures with secondary generalisation*	9.3% (5/54)	5.5% (3/55)	0.489
Simple partial seizures*	5.6% (3/54)	1.8% (1/55)	0.363
Complex partial seizures*	9.3% (5/54)	7.3% (4/55)	0.742
Anticonvulsant toxicity	5.6% (3/54)	7.3% (4/55)	1.00
Dizziness	5.6% (3/54)	7.3% (4/55)	1.00
Headache	3.7% (2/54)	5.5% (3/55)	1.00

*new or worse seizures, or seizures meeting serious adverse event criteria.

Depression symptoms resolved in 4 of the 8 patients in the DBS group over an average of 76 days (7 of the 8 patients had a prior history of depression and 3 were on antidepressant medication at baseline).
All memory impairments resolved over 12–476 days.
Neuropsychological test scores for cognition and mood did not differ between the groups at the end of the blinded phase.

Adverse events during entire study period
Deaths
There were 5 deaths during a mean follow-up of 3 years (none were during the blinded phase). 1 patient died before implantation due to probable SUDEP. In the long-term follow-up phase, 1 patient drowned and another committed suicide. One patient each in the unblinded and long-term follow-up phase died from SUDEP. None of the deaths were judged to be device-related.

There were no significant differences in seizure reduction for patients with seizure origin in frontal, parietal, or occipital regions. ***Unblinded phase and long-term follow-up*** **Median seizure frequency percentage change from baseline:** • 13 months = -41% (n = 99) • 25 months = -56% (n = 81) **Median seizure frequency percentage change from baseline (intent-to-treat):** • 13 months = -44% (n = 108) • 25 months = -57% (n = 103) **50% responder rate:** • 13 months = 43% (n = 99) • 25 months = 54% (n = 81) • 37 months = 67% (n = 42) **Liverpool Seizure Severity Scale change from baseline (lower is better):** • 13 months = -13.4 ± 21.4 (n = 103), p < 0.001 • 25 months = -12.4 ± 20.7 (n = 99), p < 0.001 **Quality of Life in Epilepsy score change from baseline (higher is better):** • 13 months = 5.0± 9.2 (n = 102), p < 0.001 • 25 months = 4.8 ± 9.3 (n = 98), p < 0.001 14 patients were seizure free for at least 6 months, 8 for at least 1 year, 4 for at least 2 years and 1 for over 4 years.	*Haemorrhage* 5 asymptomatic haemorrhages were detected incidentally by neuroimaging (study arm not reported). *Infection* 13% (14/109) of patients developed implant site infections either in the stimulator pocket, the tunnelled lead extension tract or at the site of the burr hole (study arm not reported). Another patient had a meningeal reaction. All infections were treated with antibiotics, and 9 with additional removal of hardware. 3 patients later had reimplantation. *Status epilepticus* 4.5% (5/109) of patients had status epilepticus (3 were in the stimulated group during the blinded phase and 2 were after the blinded phase). 2 were before initiation of stimulation (in patients who had missed 1 or more doses of their AEDs), 1 was during month 2 of the blinded phase, 1 occurred when the stimulator was turned on after the blinded phase and 1 occurred at month 49, 1 year after stimulation was discontinued
Abbreviations used: DBS – deep brain stimulation,	

Study 2 Salanova V (2015)

Details

Study type	Randomised controlled trial (SANTE) – Long-term efficacy and safety outcomes
Country	USA
Recruitment period	Not reported
Study population and number	n=105 All patients had DBS implants.
Age and sex	Mean age: 36 years Sex: not reported
Patient selection criteria	See Fisher R (2010) for details of inclusion and exclusion criteria for original trial. This study included all patients who entered the long-term follow-up phase beginning 13-months after implant.
Technique	See Fisher R (2010)
Follow-up	**5 years**
Conflict of interest/source of funding	Medtronic Neuromodulation sponsored the study and funded the trial.

Analysis

Follow-up issues: A total of 105 subjects entered the long-term follow-up phase beginning 13months after implant to year 5. There were 30 discontinuations in the long-term follow-up phase, including 5 deaths (1 each due to drowning, suicide, SUDEP, cardiac arrest, and liver cancer).

Study design issues: This open-label, long-term follow-up study of anterior thalamic stimulation is a continuation of SANTE trial. The follow-up reported here began at 13 months after device implantation and continued for additional 4 years. Stimulation parameters are not limited and adjusted at the investigator's discretion. Device longevity was determined through Kaplan-Meier survival analysis, and sudden unexpected death in epilepsy (SUDEP) confidence intervals (CIs) were based on the Poisson distribution. Change from baseline was tested using a paired t test or Wilcoxon signed rank test as appropriate. Seizure frequency reduction was determined via daily seizure diaries and is reported as percentage change from baseline. Sensitivity analyses were completed. The outcome measures included efficacy (seizure diary), Liverpool Seizure Severity Scale (LSSS), and 31-item Quality of Life in Epilepsy (QOLIE-31). Safety was addressed by adverse event collection and neuropsychological measures.

Study population issues: See Fisher R (2010)

Other issues: In calculating percentage for safety, the total number of patients who had DBS implants was used as a denominator (n=110).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **105**

Median total seizure frequency percent change from baseline (with at least 70 days of diary entries)

1 year	n=99	-41%	p <0.001
2 year	n=82	-56%	
3 years	n=75	-53%	
4 years	n=76	-66%	
5 years	n=59	-69%	

Seizure freedom

- 19% (11/19) seizure free
- 16% (17/109) seizure free interval of at least 6 months in the 5 years after implant
- 6 were seizure free for more than 2 continuous years during that time

Responder rate at 5 years (>=50% reduction in seizures)

- 68% (40/59)

The mean improvement from baseline in the Liverpool Seizure Severity Scale (Higher values reflect improvement)

- 1 year = 13.4 (n = 103), p < 0.001
- 5 years = 18.3 (n = 81), p < 0.001

The mean improvement from baseline in the QOLIE-31 scores (Higher values reflect improvement)

- 1 year = 5.0 (n = 102), p < 0.001
- 5 years = 6.1 (n = 80), p < 0.001

Percentage of subjects experiencing at lease a 5-point change from baseline in QOLIE-31 scores

- 1 year = 46% (n = 102)
- 5 years = 48% (n = 80)

Seizure Onset Zone:
The median reduction for temporal lobe seizures

- 1 year = 44% (n = 59), p < 0.001
- 5 years = 76% (n = 33), p < 0.001

The median reduction for frontal lobe seizures

- 1 year = 53% (n = 25), p = 0.001
- 5 years = 59% (n = 17), p = 0.005

The median reduction for all other seizure onset zones

- 1 year = 34% (n = 22), p = 0.012
- 5 years = 68% (n = 13), p = 0.124

Safety

Device-related adverse events

Adverse events	Any time after implant	5 years
Implant site pain	23.6%	20.9%
Paresthesias	22.7%	22.7%
Implant site infection	12.7%	12.7%
Therapeutic product ineffective	10.0%	8.2%
Discomfort	9.1%	9.1%
Leads not in target	8.2%	8.2%
Sensory disturbance	8.2%	8.2%
Memory impairment	7.3%	6.4%
Implant site inflammation	7.3%	7.3%
Dizziness	6.4%	6.4%
Postprocedural pain	6.4%	6.4%
Extension fracture	5.5%	4.4%
Neurostimulator migration	5.5%	5.5%

Other adverse events:

Deaths

There were 7 deaths during the study.

None were considered to be device-related.

1 probable SUDEP occurred during baseline phase(preimplant)

2 definite and 1 possible SUDEP occurred after implant

1 death due to suicide

1 death due to cardiorespiratory arrest

1 death due to liver cancer.

SUDEP rate of definite/probable SUDEP was 2.9 per 1,000 patient-years (95%CI: 0.3-10.4)

Suicide

11.8% (13 subjects) reported at least one instance of suicidal ideation (8.2% in 5 years).

1 subject committed suicide 4 years after implant, although it was judged not to be device-related.

Depression events were reported in 37.3% at some time after implant and 32.7% in 5 years. 3 events in 3 subjects were considered device related. Of 41 subjects who reported depression, 66% had a history of depression.

Previous intervention:
The median seizure reduction for subjects with or without previous vagus nerve stimulation (VNS) and previous resective surgery*

	VNS(n)	No VNS(n)	Resective surgery(n)
1 year	40% (45)	45% (54)	53% (24)
5 years	69% (25)	69% (34)	67% (14)

*p<0.001 for all values

Neuropsychological outcomes

The neuropsychological test composite scores showed significant improvement from baseline to 5 years (n=76) in attention (p<0.001), executive functions (p<0.001), depression (p=0.039), tension/anxiety (p=0.027), total mood disturbance (p=0.0016), and subjective cognitive function (p<0.001). Other scores such as verbal memory, visual memory, expressive language, and confusion were reported as statistically not significant.

Memory impairment

27.3% reported memory impairment at some time after implant and 25.5% in 5 years.

Status epilepticus

6.4% (7/109) had status epilepticus during the study.

4/7 events were non-conclusive in nature

6/7 subjects required hospitalization

3/7 events occurred in subjects who were not receiving stimulation

Abbreviations used: QOLIE- Quality of Life in Epilepsy score; VNS- Vagus Nerve Stimulation;

Study 3 Herrman H (2019)

Details

Study type	**Randomized double-blinded study**
Country	Norway
Recruitment period	2010 to 2015
Study population and number	**n=18 (8 Stimulation ON vs 10 Stimulation OFF during the blinded phase)** Adult patients with refractory focal epilepsies
Age and sex	Age range: 18-52 years; 61% (11/18) Female
Patient selection criteria	Inclusion criteria: Adults (18 to 70 years); with IQ of at least 70; focal epilepsy with or without secondary generalization. Exclusion criteria: psychogenic non-epileptic seizures, generalized epilepsy, pregnancy, other neurological diseases, serious medical conditions including psychiatric illnesses.
Technique	Performed under general anaesthesia. Stereotactic CT imaging was used for target planning. Incisions and drill holes were made bifrontally and electrodes inserted into the ANT. A Stim Lock skullcap was used to fix the electrodes in place. The final position of the electrodes was controlled with intraoperative stereotactic fluoroscopy. Medtronic DBS lead model 3389 was used. The length of the cable was 40 cm, the diameter 1.27 mm. The distance between each stimulation site was 0.5 mm and the length of the stimulating site 1.5 mm. Stimulation was given in a cyclic manner, one minute on and five minutes off, with 5 V amplitude, 90-µs duration of each stimulus and 150 Hz frequency.
Follow-up	**12 months (6 months blinded phase)**
Conflict of interest/source of funding	One of the authors received a speaker's fee from Medtronic.

Analysis

Follow-up issues: Patients were followed-up at 3,6, 9 and 12 months. One patient had her stimulation turned off after 9 months, therefore not included in the 12-month analysis.

Study design issues: A single-centre, prospective, randomized, double-blinded design. Out of 12 months study period, the first 6 months represented the double-blinded period. All 18 patients had DBS implants. After the implantation, patients were randomized to either 'stimulation ON' or 'stimulation OFF' in the operation theatre, before awakening and stimulation started at 5V for the 'ON' group. The randomization was performed by staff not involved in the study and not taking part in follow-up or evaluation of the patients. After 6 months, all patients received stimulation. Stimulation parameters were kept unchanged during the study period. Primary outcome measure was seizure frequency. Secondary outcomes were Liverpool seizure severity scale (LSSS) and adverse effects. A paired *t* test and an independent samples *t* test was used when comparing variables.

Study population issues: The active (stimulation ON) group has mean frequency seizures (all seizure types) per month of 62.1 and control group had 45.9 at baseline. At baseline, the ON group had higher FIA type seizure mean frequency per month compared to OFF group (60.6 vs 29.8), whereas mean FBTC seizure frequency per month was 1.5 for ON group and 16.1 for OFF group.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **18 (8 Stimulation ON vs 10 OFF)**

Seizure freedom after 12 months – 0/18
>50% seizure reduction after 6 months of stimulation – 22.2% (4/18)
>50% FIA seizure reduction after 6 months of stimulation – 27.8% (5/18)

Blinded phase (6months post implant):

All seizure types

	Mean Seizure frequency per month at Baseline(n)	% of baseline (SD)	*p*
ON group	62.1(8)	77% (27)	0.048
OFF group	45.9(10)	111% (128)	0.85

There was no significant difference between the 2 groups when comparing each other at 6 months (77% Vs 111%, p=0.5).

Focal impaired awareness (FIA) seizures

	Mean Seizure frequency per month at Baseline(n)	% of baseline (SD)	*p*
ON group	60.6(8)	79% (23)	0.038
OFF group	29.8(10)	91 % (159)	0.85

Focal to bilateral tonic-clonic (FBTC) seizures

Comparing only FBTC seizures in the 2 groups was not provided meaningful results, given the very small number of FBTC seizures in the active group.

Open-label phase

1 patient from OFF group was not included in the analysis after 12 months, as her stimulator was turned off after 9 months.

All seizure types

	Mean Seizure frequency per month at Baseline (n)	% of baseline (SD) after 6 months stimulation*	*p*
ON group	62.1(8)	77% (27)	0.048
OFF group	49.2(9)	78% (29)	•
All patients	55.3(17)	78% (27)	0.009

Safety

Post-operative complications

1 patient experienced twitches in the right side of his face and neck every time the stimulation cycle started. His left electrode was explanted and reinserted since the internal capsule was affected.

1 patient patient developed dysarthria and left central facial nerve palsy3 days after implantation. CT showed reduced central blood flow and cerebral blood volume, located cranially to the electrode on the right side, suggestive of infarction. She experienced total remission the following week and repeated CT and MRI were normal.

Adverse events of the stimulation

1 patient (from OFF group) had a recurrence of generalised tonic-clonic seizures when her DBS was turned on at 6 months.

1 patient reported an increase in both focal impaired awareness seizure and focal bilateral tonic-clonic seizure.

1 patient experienced a cerebral stroke 4 months after implantation. This was considered to be unrelated to the operation, but due to his condition of general health.

Other reported symptoms

Symptoms	n	Follow-up month
Headache	2	6, 9
Dizziness	1	12
Vertigo	3	9,12
Memory deficit	3	6,9,12
Transient depression	2	6,9, 12
Suicidal thoughts	1	6
Strange thoughts	1	9
Changed perception of reality	1	9
Problems finding words	1	9

Focal impaired awareness (FIA) seizures

	Mean Seizure frequency per month at Baseline (n)	% of baseline (SD) after 6 months stimulation*	*p*
ON group	60.6(8)	79% (23)	0.038
OFF group	31.3(9)	80% (35)	-
All patients	45.1(17)	79% (29)	0.009

*ON group after 6 months, OFF group after 12 months.

Compared with baseline, the seizure frequency for all seizures in the "on" group was 77% after 6 months and 83% after 12 months, indicating no trend towards any improved effect with time. Corresponding figures in the "off" group was 111% at 6 months and 78% at 12 months.

Mean Liverpool Seizure Severity Scale (LSSS)

	Pre-op (SD)	6 months (SD)	12 months (SD)	6 months stimulation*(SD)
On group	29(12)	28(12)	26(15)	28(12)
Off group	46(23)	44(21)	36(26)	36(26)
All patients	38(20)	37(19)	32(22)	33(21)

*6 months post-stimulation i.e. LSS at 6 months for ON group and at 12 months for OFF group

At baseline, the difference in mean LSS between the two groups was not significant (29 vs 46, *p*=0.058).

After the 6-month blinded phase, the difference in mean LSSS scores between the two groups were not significant (*p*=0.56)

No difference in the change in LSS between the two groups from baseline to 6 months could be detected (*p* value not reported).

The mean LSS was significantly reduced compared to baseline when all patients had experienced stimulation for 6 months (ON group after 6 months, OFF group after 12 months) (38 vs 33, *p* = 0.004).

Abbreviations used: SD – standard deviation; LSSS – Liverpool seizure severity scale;

Study 4 Cukiert A (2017)

Details

Study type	**Randomized controlled trial**
Country	Brazil
Recruitment period	2014 - 2016
Study population and number	**n= 16 (8 DBS vs 8 Control in blinded phase)** **Patients with refractory temporal lobe epilepsy**
Age and sex	Mean - 38.4 years; 69% (11/16) Female
Patient selection criteria	Inclusion criteria – refractory epilepsy (to at least three medications in monotherapy or polytherapy) for at least 2 years; TLE on MRI and video EEG; Were not considered candidates for resective surgery or declined surgery; have their medication regimen stable for at least 3 months before inclusion, and should not be taking more than four different seizure medications by the time of surgery; Seizure frequency must be at least four per month; should be able to keep a seizure diary. Exclusion criteria: had a clear history of pseudo-seizures, noncompliance, recent status epilepticus; had a progressive disease or severe systemic disease; had anatomic variations that could affect the implantation technique; had surgically resectable lesions (tumours, cavernoma, arteriovenous malformations, cortical dysplasia), had received experimental medications over the last 6 months; had already received deep brain stimulation; or could not comply with the visit's schedule.
Technique	All patients had TLE and underwent unilateral or bilateral hippocampal lead implantation under general anesthesia using quadripolar Medtronic's 3391 electrode; patients were implanted bilaterally when there was bilateral ictal onset or bilateral mesial temporal sclerosis (MTS). The electrodes were inserted using a posterior approach, using computed tomography (CT)/MRI fusion and intraoperative neuronavigation. A postoperative MRI confirmed the electrode's position in all patients. All patients received bipolar continuous nonresponsive stimulation. Stimulus duration was 300 ls and frequency was 130 Hz; final intensity was 2 V. Impedance tests were carried out on every visit. Medications were kept unaltered during the study period.
Follow-up	**6 months**
Conflict of interest/source of funding	Medtronic donated some of the stimulation hardware. Authors declared no other conflicts of interest.

Analysis

Follow-up issues: After enrolment, patients were followed for 3 months to define their preimplantation seizure frequency (M-3, M-2, M-1). After implantation, patients were allowed to recover for 1-month (M1), which was followed by a 1-month titration (or sham) period (M2). The 6-month blinded phase started immediately after M2 (Sz1, Sz2, Sz3, Sz4, Sz5, Sz6).

Study design issues: Prospective, controlled, randomized, double-blind study design. Patients were randomized on a 1:1 proportion to an active (stimulation on) or to a control (no-stimulation) arm. Seizures were counted using a seizure diary and recorded monthly after implantation. All stimulation programming was performed by a non-treating assistant. There was no sensation elicited by hippocampal stimulation, which allowed for both the patient and the treating physician to remain blinded. Patients and treating physicians were blinded during the recovery (1 month), titration (1 month), and follow-up (6 months) periods. Descriptive statistics as well as ANOVA was used for comparisons among groups and chi-square or Fisher's exact test for comparison of proportions. Outcomes measured were seizure freedom and seizure frequency reduction.

Study population issues: The 2 groups were comparable with regards to demographic and seizure history characteristics. All patients had focal impaired awareness seizures (FIAS, complex partial seizures), and 14 (87%) had focal aware seizures (FAS, simple partial seizures; 13 autonomic and one psychic). Seizure frequency ranged from 4 to 30 per month (12.5±9.4 per month). MRI findings were normal in two patients, disclosed bilateral MTS in three, left MTS in

five, and right MTS in six patients. Nine patients were receiving two different drugs, four were receiving three drugs, two were receiving four drugs, and one patient was receiving a single drug.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 16 (8 vs 8)

Seizure freedom (Seizure free over the last 2 months of blinded phase)
<table>
<tr><td>Active group</td><td>50% (4/8)</td></tr>
<tr><td>Control group</td><td>0% (0/8)</td></tr>
</table>
Responders (≥50% seizure frequency reduction)
<table>
<tr><td>Active group</td><td>88% (7/8)</td></tr>
<tr><td>Control group</td><td>38% (3/8)</td></tr>
</table>
Outcome regarding focal impaired awareness seizures (FIAS)

There was a statistically significant difference regarding FIAS frequency between the control and active groups from 1st month full stimulation (Sz1; p<0.001) to the last month of blinded phase (Sz6; p<0.001).

Outcome regarding focal impaired awareness seizures (FIAS)
There was a statistically significant difference between the control and active groups regarding FAS during the blinded phase (p < 0.006 at Sz1; p = 0.014 at Sz6), except for the Sz3 period (p = 0.249).</td><td>Two patients presented with local erosions and were treated with antibiotics. Both erosions occurred at the cranial site of the implant.

There was no other morbidity or mortality in the study.</td></tr>
<tr><td colspan="2">Abbreviations used: FAS – focal awareness seizures (simple partial seizures); FIAS – focal impaired awareness seizures (complex partial seizures)</td></tr>
</table>

Study 5 Chang B (2017)

Details

Study type	**Systematic review and meta-analysis**
Country	Not reported for individual studies
Recruitment period	Search date: August 2016; Search period: 1990- 2016.
Study population and number	**n=61** 8 studies (case-control studies) with refractory temporal lobe epilepsy patients
Age and sex	Mean age at DBS: 32.3 (only 6 studies reported mean age) Sex: Not reported
Study selection criteria	Study inclusion criteria: postoperative seizure outcomes of DBS collected from at least four patients with refractory temporal lobe epilepsy, a mean or median follow-up of ≥1 year, outcomes measured with seizure frequency reduction scale or comparable rubric. Exclusion criteria: studies with <4 cases. If studies had overlapping patient populations, only one of the studies (the most recent one) was included.
Technique	Surgical techniques, targets, stimulation parameters and stimulation period varied across studies, but not reported in detail in this systematic review.
Follow-up	**Mean – 3.3 years**
Conflict of interest/source of funding	Authors declared no conflicts of interest.

Analysis

Follow-up issues: Follow-up ranges from 1.5 years to 8.5 years in studies.

Study design issues: Two authors conducted comprehensive literature search and performed data extraction independently. All included studies were case-controlled studies. The quality of each included study was evaluated with the modified Newcastle-Ottawa scale (NOS). The primary outcome was remarkable seizure reduction (RSR), defined as seizure frequency reduction of at least 70%, in the last reported follow-up. The RSR rates from the analysed studies were pooled. The degree of heterogeneity across the analysed studies was assessed with Q statistics. Publication bias was assessed with funnel plots.

Study population issues: The duration of temporal lobe epilepsy varied significantly across studies, ranging from 11 years to 26 years.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **61**

Seizure reduction

Study	n	RSR rate
Velasaco 2007	9	66.7% (6/9)
Cukeirt 2013	9	55.5% (5/9)
Lim 2015	5	20.0% (1/5)
Osorio 2007	4	50.0% (2/4)
Boon 2007	10	20.0% (2/10)
Ding 2016	5	60.0% (3/5)
Vonk 2013	11	63.6% (7/11)
Bonndallaz 2013	8	62.5 (5/8)
Pooled	**61**	**59% (95% CI, 45-72%)***

*I^2 = 0%

	RSR	OR (95%CI) *	*p*
Male	47.8% (11/23)	0.45(0.12-1.65)	0.23
Female	64.7% (11/17)		
Unilateral EEG ictal	92.3% (24/26)	8.43(1.68-42.19)	0.005
Bilateral EEG ictal	44.4% (8/18)		
Partial Seizure	63.6% (7/11)	1.90(0.40-8.98)	0.42
Generalised seizure	50% (8/16)		
Normal MRI	64.5% (20/31)	1.23(0.42-3.61)	0.71
Abnormal MRI	57.1% (12/21)		

*M.H, Fixed OR

Association between continuous variables and RSR

Variables	WMD (95% CI)	*p*
Age at seizure reduction	2.61 (0.96-4.25)	0.002
Age at surgery	3.20(2.40-8.81)	0.26
Epilepsy duration	0.12(3.97-4.20)	0.96

Remarkable seizure reduction (RSR) was associated with a later age of seizure onset, but not associated with patient's age at DBS or Epilepsy history duration.

Safety

NO SAFETY DATA

Abbreviations used: RSR – remarkable seizure reduction, defined as a seizure frequency reduction of at least 70% in the last reported follow-up. CI- confidence interval.

Study 6 Sprengers M (2017)

Details

Study type	Cochrane systematic review and meta-analysis
Country	Individual studies from USA, Canada, Mexico and Germany
Recruitment period	Search date: November 2016
Study population and number	**n= 45** (7 studies, excluding cerebellar stimulation and responsive neurostimulation and the SANTE trial) 2 studies (n=20) on DBS for centromedian thalamic nucleus stimulation 4 studies (n=21) on DBS for Hippocampal stimulation 1 study (n=4) on DBS for Nucleus accumbens stimulation The review reported both DBS and cortical stimulations, however, only studies with DBS were selected for this overview.
Age and sex	Range:4-65 Sex – not reported
Study selection criteria	Selection criteria: Randomized controlled trials investigating deep brain stimulation (and cortical stimulation) in patients with refractory epilepsy were selected. Blinded as well as unblinded studies were considered for selection. Both patients with normal and abnormal MRIs were included. Only RCTs comparing active vs sham stimulation, resective surgery, further treatment with antiepileptic drugs or other neurostimulation treatments (including vagus nerve stimulation) were included. Exclusion criteria: Non-randomized controlled trials, non-refractory epileptic patients, intracranial stimulation for other purposes, ongoing and still recruiting studies.
Technique	DBS techniques varied across the studies; Different individual studies involved different stimulation targets, both unilaterally and bilaterally. Details surgical or programming techniques for the individual studies were not reported.
Follow-up	**Overall follow-up not reported. Follow-up ranged from 2 months to 84 months**
Conflict of interest/source of funding	One of the authors is supported by an “FWO-aspirant” grant (Research Foundation Flanders). Another author is supported by a BOF-ZAP grant from Ghent University Hospital. Another author is supported by grants from FWO-Flanders, grants from BOF, and by the Clinical Epilepsy Grant from Ghent University Hospital. Medtronic Inc has provided support in terms of free devices for a pilot study and an international multicentre randomized trial of hippocampal deep brain stimulation in epilepsy co-ordinated by Ghent University Hospital.

Analysis

Study design issues: Cochrane systematic review and meta-analysis of RCTs. Comprehensive search strategy was used. Four review authors independently selected trials for inclusion. The outcome investigated were seizure freedom, responder rate (>50% reduction in seizure frequency), percentage seizure frequency reduction, neurophysiological outcomes, quality of life and adverse events. Subgroup analysis of target stimulation was performed.

Study population issues: The studies included in subgroup analysis have heterogeneous and included patients with different type epilepsy (left medial temporal, bitemporal et) and normal or abnormal MRI.

Other issues: This review included SANTE trial in their analysis, however, the trial is separately reported in this overview. Therefore, we have not reported the outcomes for the trial from this study. We have also excluded the cortical stimulation and responsive neuro stimulation results from the study. The 4 cross-over trials included in the study did not have any or a sufficient washout period, complicating interpretation of the results due to carryover effect.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **45**

Cnetromedian thalamic nucleus stimulation

Outcomes	Number of studies	Number of patients/treatment periods*		OR/Mean difference (95% CI)	p
		Active	Sham		
Seizure freedom	1	6	6	1.00(0.11, 9.39)	1.00
Responder rate	1	6	6	1.00(0.27,3.69)	1.00
Seizure frequency reduction	1	6	6	7.05(-44.05,58.15)	0.79

There were two studies selected for centromedian thalamic nucleus stimulation. However, only one study was included in the meta-analysis as the other study provided graphs only without exact figures. The qualitative analysis from the excluded study showed that there was 1 patient seizure free and 11 out of 13 had ≥ 50% seizure reduction at the maximum open-label follow-up. For seizure frequency reduction, graphs showed approximately a mean 75% reduction during stimulation 'on' as well as 'off' periods for this cross-over trial (p=0.23).

Hippocampal (1 to 3 months blinded phase)

Outcomes	Number of studies	Number of patients/treatment periods*		Pooled OR/Mean difference (95% CI)	p
		Active	Sham		
Seizure freedom	3	10	11	1.03(0.21,5.15)	0.97
Responder rate	3	10	11	1.20 (0.36,4.01)	0.76
Seizure frequency reduction	3	10	11	-28.14 (-34.09, -22.19)	<0.00001
Quality of life	1	3	3	-5.00(-53.25, 43.25)	0.84

Hippocampal (4 to 6 months blinded phase)

Outcomes	Number of studies	Number of patients/treatment periods*		OR/Mean difference (95% CI)	p
		Active	Sham		
Seizure freedom	1	2	4	1.80(0.03,121.68)	0.78
Responder rate	1	2	4	9.00(0.22, 362.46)	0.24

Nucleus accumbens stimulation

Outcomes	Number of studies	Number of patients/treatment periods*		OR/Mean difference (95% CI)	p
		Active	Control		
Seizure freedom	1	4	4	1.00(0.07,13.64)	1.00
Responder rate	1	4	4	10.00(0.53,189.15)	0.12
Seizure frequency reduction	1	4	4	-33.80(-117.37, 49.77)	0.43
Quality of life	1	4	4	2.78(-7.41, 12.97)	0.59

*Treatment period for cross-over studies

Neuropsychological outcomes

Centromedian thalamic nucleus stimulation

- No significant differences in any of the neuropsychological tests were observed between baseline and stimulation 'on' and 'off' periods.

Hippocampal stimulation (1 to 3 months of stimulation)

- Neuropsychological test results were the same or very similar during stimulation ON and OFF periods in one study(n=4). In another study (n=2), 1 patient worse verbal and visuospatial memory scores when stimulated (values not provided), despite reported subjective memory improvement during the same period.

Hippocampal stimulation (4 to 6 months of stimulation)

- At 7 months, scores of cognitive scales assessing recall (Rey Auditory Verbal Learning Test, Rey Complex Figure Test) were generally lower in the active stimulation compared to the sham group (p>0.05)

Nucleus accumbens stimulation

- Neurocognitive test scores were similar and not statistically different during sham and active stimulation

Safety

Cnetromedian thalamic nucleus stimulation (n=20)

Adverse events	n	Comments
Haemorrhage	1	Asymptomatic minimal haemorrhage on post-operative CT
Skin erosions	3	all 3 (2 young children) required explanation.
Other	1	Repair of the connection to the pulse generator

Hippocampal stimulation (n=21)

Adverse events	n	Comments
Skin erosions and local infection	3	all 3 required explanation.

Nucleus accumbens stimulation(n=4)

Adverse events	n	Comments
Local infection	1	a local subcutaneous infection two weeks post-surgery requiring antibiotics and hardware removal.
Increased seizure frequency	1	increased frequency of disabling seizure during both sham and active stimulation period
First-time generalized tonic-clonic seizure	1	during sham stimulation period
Loss of interest	1	during both sham and active stimulation period
sleep disturbance	2	one patient had during both sham and active stimulation, one had only during sham stimulation
depressive mood	1	during sham stimulation period
Listlessness	1	during sham stimulation period

Study 7 Yan H (2019)

Details

Study type	**Systematic review**
Country	Individual studies from Mexico, South Africa, France, Colombia, Brazil, China, UK, US, South Korea, Taiwan, Spain
Search period	Inception to November 2017
Study population and number	**n=40 (21 studies)** Children (age ≤ 18 years) with drug-resistant epilepsy
Age and sex	Age range: 4 to 18 years; 63% (19/30) male (sex not reported for 10 patients).
Patient selection criteria	Inclusion criteria: diagnosis of drug-resistant epilepsy, as defined by the individual studies, treatment with DBS, inclusion of at least 1 paediatric patient and; patient specific data. Exclusion criteria: missing data for age, DBS target, or seizure freedom; non-human subjects, editorials, abstracts, review articles and dissertations.
Technique	Detailed surgical technique was not reported. Various DBS targets were used.
Follow-up	**Range: 0.5 to 84 months**
Conflict of interest/source of funding	One of the authors had speaker's honorarium from Medtronic.

Analysis

Follow-up issues: 2 of the patients had DBS implants only for 2 weeks to determine the location and extent of epileptic focus before a temporal lobectomy. The follow-ups for the individual studies were heterogenous but the 60% of patients (n=24) had at least 18 months of follow-up.

Study design issues: The review was conducted according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) guidelines. A comprehensive search strategy was used. Two independent reviewers systematically reviewed and extracted data and any disagreements were resolved by consensus. Primary outcome measures were seizure freedom (International League Epilepsy class I) and Seizure frequency reduction from baseline. The outcomes were reported for individual patients. No meta-analysis or pooled analysis was done.

Study population issues: Patients included in the individual studies had a wide range etiologies and types of seizures.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 40

Seizure Freedom
12.5% (5/40) had an International League Epilepsy class I (i.e. seizure free)

Seizure reduction*
<table>
<tr><th>DBS location</th><th>% of patients with seizure reduction</th><th>Mean % of seizure frequency reduction from baseline(range)</th></tr>
<tr><td>Centromedian nucleus</td><td>94.4% (17/18)</td><td>71.6% (0-100)</td></tr>
<tr><td>ANT</td><td>75.0% (6/8)</td><td>51.8 (0-90)</td></tr>
<tr><td>Hippocampus</td><td>60.0% (3/5)</td><td>48.8% (0-100)</td></tr>
<tr><td>Subthalamic nucleus</td><td>66.7% (2/3)</td><td>26.9% (0 - 80.7)</td></tr>
<tr><td>Posteromedial Hypothalamus</td><td>100.% (2/2)</td><td>94.8% (89.6-100)</td></tr>
<tr><td>Mammillothalamic tract</td><td>100% (2/2)</td><td>93% (86-100)</td></tr>
<tr><td>Caudal Zona Inserta</td><td>100% (1/1)</td><td>100%</td></tr>
<tr><td>Overall</td><td>85.0% (34/40)</td><td>65.8% (0-100)</td></tr>
</table>
*DBS locations were either unilateral or bilateral. Follow-up for these outcome ranges from 0.5 to 84 months. For some patients, seizure reduction was reported separately for different types of seizures (e.g. complex and simple seizure) but only the lower number was used for this overview. Seizure reduction for one patient was reported in range (80-90%), but the mid-point 85% was used for this overview. Mean % of seizure frequency was not reported in the systematic review. It was calculated using the seizure reduction for individual patients.</td><td>Adverse events
Total 4 adverse events reported in 4 patients.

Infection, n=1
Patient required explanation due to infection of the anterior chest

Skin erosion, n=2
2 patients required explanation due to skin erosion of batteries

Electrode lead breakage, n=1
Patient had electrode lead breakage after 34 months requiring battery and electrodes replacement</td></tr>
<tr><td colspan="2">Abbreviations used: ANT – anterior nucleus of the thalamus</td></tr>
</table>

Study 8 Valentin A (2013)

Details

Study type	**Non-randomized comparative study**
Country	UK and Spain (two centres)
Recruitment period	Not reported
Study population and number	**n=11 (6 generalised epilepsy, 5 frontal epilepsy)** Adults with generalized or frontal lobe seizure.
Age and sex	Mean: 37 years; 82% (9/11) male
Patient selection criteria	Inclusion criteria: age >18 years; clear diagnosis of epilepsy (confirmed by scalp or intracranial telemetry); patients were unsuitable for resective surgery; seizure frequency ≥10/month; patients were able to give informed consent; patients or carers were able to keep seizure diaries; and patients were on stable dose of AEDs. Exclusion criteria: major neurologic or psychiatric disorders; history of poor compliance with medication; temporal lobe epilepsy; and previous intracranial surgery.
Technique	Deep brain stimulation of the bilateral centromedian thalamic nucleus. One four-contact electrode (K-3387 or K-3389, Medtronic) was implanted stereotactically in the CMN of each hemisphere under general anaesthesia. Electrodes were implanted through bilateral frontal burr holes in a transparenchymal extraventricular trajectory under neurophysiologic monitoring. The position of implanted electrodes was checked with intraoperative MRI or CT.
Follow-up	**Mean: 2 years**
Conflict of interest/source of funding	AV received funding for travel, expert advice, and speaker honoraria from Medtronic. RS and RC received speaker honoraria from Cyberonics.

Analysis

Follow-up issues: One patient had only 6 months of follow-up because he had the device removal due to infection. Remaining 10 patients had follow-up range from 20 to 72 months.

Study design issues: A two-centre, single-blind, non-randomized, controlled (cross-over) study. The study was divided in five stages: baseline (3 months pre-implantation), electrode implantation, parameter optimization with system internalization (1 week) , blind period (Stimulation-OFF 3 months and Stimulation-ON 3 months), and open label follow-up. Single blinding was done by telling patients that they would be randomized to 3 months of stimulation ON and 3 months of stimulation OFF, or vice versa, but they all had 3 months OFF period first, as a 'washout period' for the effects of implantation. The primary outcome measure was the frequency of major seizures (generalised tonic-clonic seizures, the complex partial seizures with or without secondary generalization). Patient reported outcome measures (Quality of Life in Epilepsy-Patient Weighted [QOLIE-31-P], Seizure Severity Scale, Hospital Anxiety Disorders) were also collected before and 6 months after implantation. Fisher exact test was used to assess differences in seizure frequency reduction between frontal and generalised epilepsy groups. Wilcoxon matched-paired signed-rank test was used to compare before and after PRO values.

Study population issues: 4 patients had idiopathic generalized epilepsy, 2 patients had presumed symptomatic generalized epilepsy and 5 patients had frontal lobe epilepsy. Among the two frontal lobe epilepsy patients, 2 had mild cortical atrophy in imaging, all other patients had normal imaging. All generalized patients were on polytherapy AEDs. 1 frontal love patient was on monotherapy, 1 on two AEDs and 3 on polytherapy.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 11
Seizure freedom

2 patients with generalised epilepsy became seizure free immediately after implantation and remained seizure free until 12 months. Stimulation for both patients remained OFF during the whole seizure free period. 1 of the patients remained seizure free for the whole follow-up period (60 months) and the other patient was seizure free for 12 months.
None of the frontal epilepsy patients had seizure freedom during the follow-up period.

Responder rate (≥50% reduction in seizure frequency from baseline)
<table><tr><td>Follow-up (months after implantation)</td><td>Generalised epilepsy</td><td>Frontal epilepsy</td><td>p</td></tr><tr><td>3 months (DBS OFF)</td><td>100% (6/6)</td><td>20 % (1/5)</td><td>0.015</td></tr><tr><td>6 months</td><td>100% (6/6)</td><td>20 % (1/5)</td><td>0.015</td></tr><tr><td>12 months</td><td>83% (5/6)</td><td>0 % (0/4)</td><td>0.048</td></tr></table>
In the long-term extension phase of generalised epilepsy (follow-up range 20 to 72 months), 83% (5/6) of showed ≥50% reduction in seizure frequency, including 3 seizure free.

In the long-term extension phase of frontal epilepsy (follow-up range 22 to 48 months), 50% (2/4) (patients had ≥50% reduction in seizure frequency.

Patient-related outcomes
<table><tr><td></td><td>n</td><td>Pre-DBS: Median score(range)</td><td>6 months post-DBS: Median score (range)</td><td>p</td></tr><tr><td>QOLIE-31-P total</td><td>7</td><td>53.9(24.8-68.5)</td><td>68.8(43.9-75.9)</td><td>0.018</td></tr><tr><td>QOLIE-31-P distress</td><td>7</td><td>53.6 (7.1-72)</td><td>75(.9.3-92.9)</td><td>0.075</td></tr><tr><td>HADS</td><td>7</td><td>17 (0-18)</td><td>7(0-17)</td><td>0.24</td></tr><tr><td>SSQ</td><td>5</td><td>3.12 (0.9-17.1)</td><td>3.46(1.1-18.1)</td><td>0.043</td></tr></table></td><td>Infection
1 patient (9.1% of total patients) had device removed 6 months after implantation due to infection.

Transitory agraphia
1 patient (9.1% of total patients) experienced transitory agraphia 4 days after implantation, which resolved later.

Other side effects
Most patients reported tingling sensation in the contralateral arm at the time device activation, but symptoms disappeared within minutes (number of patients not reported).

No death reported.
No patient showed post-surgical haemorrhage or oedema.
No patient required repositioning of electrodes.</td></tr>
<tr><td colspan="2">Abbreviations used: QOLIE-31-P, quality of life in epilepsy version 31P; HADS, Hospital Anxiety and Depression Scale; SSQ, seizure severity questionnaire;</td></tr>
</table>

Study 9 Kim (2017)

Details

Study type	**Case series (retrospective study)**
Country	Korea
Recruitment period	2005 - 2015
Study population and number	n=29 Patients with refractory epilepsy patients
Age and sex	Mean age: 30.7 years; 62.1% (18/29) male
Patient selection criteria	Inclusion criteria: frequent (>4 per month) and disabling seizures not controlled by multiple AED treatment modalities; not a candidate for resective surgical treatment as determined by video-EEG monitoring (e.g. multifocal ictal onset zone); previously failed resective or disconnection surgery; Patients without mental retardation (IQ >70). Exclusion criteria: Not reported.
Technique	Each patient underwent frame-based, microelectrode-guided, stereotactic implantation of DBS leads (Medtronic® model 3389 or 3387) with either local or general anaesthesia using a Leksell frame. Electrode placement was confirmed with post-operative CT or MRI. Activation and programming started 1 or 2 weeks after implantation. The initial parameters were high frequency of 130 Hz; pulse width of 90 microseconds; continuous stimulation, but later adjusted to relatively low voltage (1.5 - 3.1 V) stimulation and monopolar configuration based on improvement in seizure frequency.
Follow-up	**Median: 70 months (range 18 - 137 months)**
Conflict of interest/source of funding	None

Analysis

Follow-up issues: Initially, 30 patients' records were studied retrospectively, but 1 patient withdrew 2 months after surgery due to implant site infection and removal of all DBS devices. Of the 29 patients in the analysis, 26 patients completed at least 2 years of follow-up, 24 completed 3 years, 20 completed 5 years, 12 completed 7 years, 10 completed 9 years and 2 completed 11 years. There were eight discontinuations of stimulation in the long-term follow-up period, including four deaths, three due to lack of efficacy, and one due to complaints of increased agitation despite his meaningful seizure reduction.

Study design issues: Retrospective, bi-institutional case series. The data were collected via retrospective review of the medical records of 29 consecutive patients with refractory epilepsy who underwent ATN DBS between 2005 and 2015, Follow-up evaluations were conducted during routine outpatient clinic visits, hospital visit for reoperation or scheduled battery changes, and via telephones interviews. Primary outcome measures were

Study population issues: The patients' mean age at symptom onset was 11.9± 8.6 years, and the median age at surgery was 29 years (range,15–55 years). The mean duration of epilepsy was 19.3± 9.0 years, and most patients were undergoing AED polytherapy (4.3±2.7 regimens) and had failed several AEDs (5.2±4.1 drugs) in the past.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **29**

Seizure freedom:

24.1% (7/29) were seizure free for at least 6-months.

13.8% (4/29) had extended periods of seizure freedom at least 1 year or longer.

Median percent seizure frequency reduction compared to baseline

Follow-up	n	Media % reduction	Range	p
1 Year	29	70.0 %	-20.0 to 100%	<0.001
2 Years	26	73.6%	-87.5 to 100%	
3 Years	24	78.4%	8.3 to 100%	
4 Years	20	70.8%	25.0 to 100%	
5 Years	20	70.9%	-5.6 to 100%	
6 Years	16	70.8%	0 to 100%	
7 Years	12	66.7%	-5.6 to 100%	
8 Years	10	68.4%	-25.0 to 100%	
9 Years	10	66.7%	-5.6 to 100	
10 Years	3	66.7%	10.0 to 100%	
11 Years	2	66.7%	40.0 to 83.5%	

Overall median seizure frequency reduction (compared to baseline frequency) at years 1 through years 11 was 70.0%.

Responders rate (>50% reduction in seizure frequency):

Follow-up	Responders rate*
1 Year	75.9%
2 Years	75.9%
3 Years	80.8% (21/26)
4 Years	85.0% (17/20)
5 Years	73.7%
6 Years	75.0% (12/16)
7 Years	78.6%
8 Years	70.0% (7/10)
9 Years	70.0%
10 Years	66.7% (2/3)
11 Years	50.0%

*Number of patients not reported for all patients

Overall, 76.0% (22/29) were responders and 24.0% (7/29) were non-responders during the follow-up period.

Median seizure reduction by type of seizure onset origins

Temporal lobe seizure:

- 1 Year = 71.5 % (n= 9), p<0.001
- 7 Years = 70.0 % (n= 3), p<0.001

Frontal lobe seizure:

- 1 Year = 74.1 % (n= 8), p<0.001
- 10 Years = 83.9 % (n= 3), p<0.001

All other onset origin:

- 1 Year = 42.6 % (n= 12), p<0.05
- 10 Years = 67.6 % (n= 3), p<0.01

Neuropsychological outcomes (Number of patients = 12)

Outcomes	Baseline (Mean ± S.D.)	Post DBS – Baseline (Mean)*	*p*-value
IQ			
Verbal IQ	87.5 ± 14.3	0.8	0.53
Performance IQ	86.5 ± 14.7	0.5	0.75
Total IQ	86.3 ± 14.7	1.4	0.09
Rey-Kim Memory Test (RKMT)			
Immediate verbal recall	6.6 ± 1.9	0.91	**0.043**
Delayed verbal recall	5.4 ± 3.8	2.5	**0.004**
Rey figure drawing	9.1 ± 5.2	0.6	0.37
Rey figure immediate recall	5.3 ± 4.1	1.2	**0.011**
Rey figure delayed recall	5.4 ± 4.0	0.4	0.18
MQ (memory quotient)	73.9 ± 20.3	8.1	**0.011**
Korean version of Memory Assessment Scales (K-MAS)			
Short term memory	73.6 ± 19.9	1	0.76
Verbal memory	75.3 ± 16.3	5.5	0.09
Visual memory	78.9.6 ± 18.6	2.3	0.55
Full memory	75.0 ± 15.8	6	0.041
Frontal lobe function and attention			
MMSE	24.8 ± 4.1	0.4	0.39
Trail Making Test			
Time on part A	78.5 ± 72.5	3.9	0.82
Time on part B	125.8 ± 107.7	−8.5	0.75
Digit Span forward	6.1 ± 1.9	−0.3	0.46
Digit Span backward	3.8 ± 1.7	0	1.00
Word fluency test			
Category	19.8 ± 8.5	4.3	**0.010**
Letter	20.2 ± 12.3	8.1	**0.013**
Digit Symbol	7.3 ± 3.1	0.3	0.67
Pegboard test			
Right hand	199.8 ± 196.5	2.8	0.77
Left hand	204.5 ± 203.7	−17.5	0.40

*Changes from baseline to the end of the long-term phase (NP testing score at least 12 months after baseline evaluation).

Adjustment of anti-epileptic drugs (AED)

AED were adjusted only after 2nd year of follow-up if necessary.

9.1% (2/22) of the responders and 71.4% (5/7) of the non-responders added at least 1 new AED during the follow-up($p<0.05$).

22.0% (5/22) of the responders and 14.3% (1/7) of the non-responders had a reduction of dosage or number of AEDs.

Safety

Deaths

There were 4 deaths during the follow-up period.

1 (3.4%) probable sudden unexplained death in epilepsy (SUDEP) occurred 5 years after implantation.

1 committed suicide.

1 cardiorespiratory arrest from septic shock from non-neurological cause.

1 died from severe intracranial haemorrhage from a traffic accident.

Haemorrhage, n=1

Patient had intracranial haemorrhage who experienced left hemiparesis immediately after DBS lead insertion. The weakness resolved after 3 months with physical therapy.

Infection, n=2

1 patient from the initial recruitment of 30 patients had post-operative deep infection, requiring device removal, intravenous antibiotics and subsequent exclusion from the follow-up.

1 patient from the remaining 29 enrolled had a superficial infection in the wound site on the chest requiring short-term antibiotics.

Revision of lead location, n=3

3 patients required revision surgery to revise lead position. Overall, there was 5.2% (3/58 implanted leads) incidence of lead revision for malposition.

Lead fracture or hardware malfunction

6.9% (2/29) of patients had to return to the operating theatre to replace a fractured lead.

Depression and suicide

- Depression - 17.2% (5/29)
  7 depressive episodes from 3 patients were considered device-related. 60% (3/5) had a history of depression.
- Suicidal ideation - 6.9% (2/29)
- Suicide - 3.4% (1/29)
  Patient committed suicide approximately 7.5 years after implantation, not judged by the investigator to device-related.

Subjective memory impairment

24.1% (7/29) reported subjective memory impairment at some point during the follow-up period. 5 patients completed neuropsychological testing and only 1 had a confirmed change from baseline.

Study 10 Troster A (2017)

Details

Study type	**Randomized controlled study (SANTE) – Follow-up study for mood and memory outcomes**
Country	USA
Recruitment period	
Study population and number	**n=67** 67 from SANTE trial entered 7-year follow-up
Age and sex	See Fisher R (2010). Not reported separately for long-term follow-up.
Patient selection criteria	See Fisher R (2010)
Technique	See Fisher R (2010)
Follow-up	**7 years**
Conflict of interest/source of funding	Medtronic, Inc sponsored the study and funded the trial. One author is an employee for Medtronic and also holds stock options from Medtronic. Another author received honoraria/or is on the scientific advisory board of St Jude Medical, Medtronic, Boston Scientific, Michael J. Fox foundation.

Analysis

Follow-up issues: 67 out of 108 subjects from the original trial completed 7 years follow-up. Not all 67 had every neurobehavioral functioning test at both baseline and follow-up.

Study design issues: This long-term follow-up study of memory and mood outcomes was a continuation study of SANTE trial. The study reported the effects of ANT stimulation mood and cognition over 7-year period. The study also reported memory and depression events for the blinded phase of the trial (4 months post-implants), however, only 7-year follow-up results were included in this overview. The blinded phase results for the trial are included in Fisher R (2010) and Salanova V (2015).

Study population issues: See Fisher R (2010).

Other issues: The neurocognitive outcome from the blinded phase were reported separately in this overview (See Fisher R (2010) and Salanova V (2015). Only results from the 7 years follow-up were included in this overview.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **67**

Change in Neurobehavioral functioning scores from baseline to Year 7

Test	N	Baseline	Year 7	Change	Wilcoxon
		Mean ± Std	Mean ± Std	Mean ± Std	p-Value
Visual motor speed					
D-KEFS Trailmaking Motor Speed (ss)	67	8.9 ± 3.5	9.5 ± 3.1	0.6 ± 2.9	0.104
Verbal memory					
CVLT Trials 1–5 Total (T)	66	41.5 ± 11.2	41.7 ± 11.9	0.2 ± 10.9	0.758
CVLT Long Delay Free Recall (z)	66	−1.4 ± 1.5	−1.2 ± 1.4	0.2 ± 1.2	0.347
CVLT Recognition Hits (z)	66	−1.1 ± 1.4	−1.0 ± 1.4	0.1 ± 1.8	0.707
CVLT Discriminability (z)	66	−0.8 ± 1.3	−0.8 ± 1.2	−0.1 ± 1.3	0.423
Visuospatial memory					
BVMT-R Total Recall (T)	66	35.2 ± 11.9	38.1 ± 13.2	2.9 ± 10.1	**0.012**
BVMT-R Delayed Recall (T)	66	37.8 ± 13.4	38.2 ± 14.6	0.4 ± 12.3	0.624
BVMT-R Recognition Hits (z)	65	5.5 ± 0.8	5.4 ± 0.8	−0.1 ± 0.9	0.272
BVMT-R False Alarms (z)	65	0.2 ± 0.9	0.2 ± 0.6	0.0 ± 1.1	0.603
Language					
D-KEFS Verbal Fluency: Category Fluency (ss)	66	5.6 ± 3.7	5.3 ± 3.6	−0.3 ± 3.4	0.408
D-KEFS Verbal Fluency: Letter Fluency (ss)	66	6.3 ± 3.4	6.9 ± 3.1	0.6 ± 2.3	0.053
Design fluency					
D-KEFS Design Fluency—Total Correct (ss)	66	8.7 ± 2.8	10.5 ± 2.9	1.8 ± 2.8	**<0.001**
Executive function					
D-KEFS Trailmaking Number–Letter Switching (ss)	67	7.5 ± 3.9	8.6 ± 3.7	1.1 ± 3.7	**0.019**
D-KEFS Inhibition/Switching (ss)	64	6.8 ± 4.0	7.9 ± 4.0	1.1 ± 3.6	**0.015**
D-KEFS Tower Test Total (ss)	65	8.7 ± 3.1	12.9 ± 3.2	4.1 ± 3.3	**<0.001**
D-KEFS Verbal Fluency: Category Switching (ss)	65	6.7 ± 3.8	6.2 ± 3.3	−0.5 ± 3.6	0.325
Patient subjective cognitive function					
POMS Confusion/Bewilderment (T)	66	59.6 ± 10.8	59.6 ± 12.0	0.0 ± 11.0	0.876
FrSBe Executive Dysfunction (T)	66	66.3 ± 18.2	63.9 ± 17.6	−2.4 ± 16.7	0.299
FrsBe Total (T)	66	66.9 ± 19.4	64.0 ± 18.1	−2.9 ± 16.6	0.178
Depression and apathy					
POMS Depression (T)	66	56.4 ± 11.8	56.5 ± 12.2	0.1 ± 11.6	0.964
FrSBe Apathy (T)	66	67.3 ± 16.0	64.6 ± 17.1	−2.7 ± 15.2	0.13
Patient subjective behavioral disturbance					
FrSBe Disinhibition (T)	66	57.5 ± 16.9	55.8 ± 16.0	−1.7 ± 15.8	0.336
Patient subjective fatigue and energy					
POMS Fatigue (T)	66	55.4 ± 11.8	53.8 ± 10.4	−1.6 ± 10.7	0.245

POMS Vigor (T)	66	43.3 ± 7.5	44.0 ± 10.1	0.6 ± 8.7	0.521
Anxiety					
POMS Tension (T)	66	58.3 ± 11.1	56.0 ± 12.4	−2.3 ± 11.8	0.226
Visual attention					
D-KEFS Trailmaking Visual Scanning (ss)	67	7.9 ± 3.4	8.0 ± 3.9	0.1 ± 3.4	0.663
D-KEFS Trailmaking Letter Sequencing (ss)	67	7.8 ± 3.8	9.3 ± 3.6	1.5 ± 3.3	**<0.001**
D-KEFS Trailmaking Number Sequencing (ss)	67	7.9 ± 3.3	9.6 ± 3.8	1.7 ± 3.1	**<0.001**
Processing speed					
D-KEFS Color-word Interference Color Naming (ss)	66	7.0 ± 3.8	7.3 ± 3.7	0.3 ± 2.9	0.395
D-KEFS Color-Word Interference Word Reading (ss)	66	6.9 ± 3.8	7.0 ± 3.8	0.1 ± 3.1	0.453

Seven-year follow-up on 67 subjects form SANTE trial reveal no significant cognitive declines, neurobehavioral problems, subjective cognitive declines, or affective distress (depressive and anxious symptoms) among the group.

Significantly better test scores compared to baseline were observed at 7 years in immediate visual recall (p=0.012), design fluency (p<0.001), Executive functions such as Trailmaking (Number–Letter Switching) (p=0.019), an analog of the Stroop task (Inhibition/Switching)(p=0.015), the Tower task (problem solving)(p<0.001), and simple visual attention (Trailmaking Number Sequencing and Letter Sequencing) (p<0.001 for both).

Abbreviations used: BVMT-R, Brief Visuospatial Memory Test – Revised; D-KEFS, Delis-Kaplan Executive Function System;

Study 11 Hamdi H (2019)

Details

Study type	**Case report**
Country	France
Recruitment period	Not reported
Study population and number	**n=1** Patient with refractory epilepsy
Age and sex	32 years; male
Patient selection criteria	Not applicable
Technique	Deep Brain Stimulation for Epilepsy targeting bilateral anterior nucleus of the thalamus (ANT) was performed using a stereotactic frame. MRI and CT with contrast were used to identify the target. To topography of both ANY was identified, and the third ventricle was very narrow challenging the operation. In the operation, under general anaesthesia, the electrodes were implanted via paramedian coronal holes. Stimulation was switched on 1 month after implantation. Stimulatory parameters were 3V, 130Hz and 60 microseconds on the second last lead contact bilaterally.
Follow-up	**4 months**
Conflict of interest/source of funding	None

ANT stimulation induced relapsing encephalitis

Patient with history of herpes meningoencephalitis at the age of 7 months had ANT-DBS for refractory epilepsy. The stimulation was turned on 1 month after implantation. Patient presented to the emergency with mild confusion and hallucination on the second day after the stimulation was turned on. He was treated empirically. Four days after, he presented to the emergency unit again with confusion, hallucination, mild apraxia, headache, retrograde amnesia and fever. MRI showed a left temporal-mesial hypersignal. Microbiology test was positive for herpes simplex virus type 1 (HSV-1) confirming the diagnosis of Herpes simplex encephalitis.

Patient's clinical conditions improved with anti-viral medication. Seizure disappeared even after the stimulation had been stopped for 4 months, then returned as before.

Study 12 Son B (2018)

Details

Study type	**Case report**
Country	Korea
Recruitment period	2015
Study population and number	**n=1** patient with bilateral ANT-DBS for refractory epilepsy
Age and sex	45 years; male
Patient selection criteria	Not applicable
Technique	Revision of DBS lead and replacement of implantable pulse generators under general anaesthesia.
Follow-up	**Not reported**
Conflict of interest/source of funding	None

Cerebrospinal fluid egress from the DBS electrode

Patient, who had ANT-DBS for 5 years, presented with increasing seizure frequency and a shortened battery longevity within 2 years. MRI showed left sided DBS lead was in the third ventricle leaning on the medial wall of ANT. Electrode revision was performed. Upon disconnecting the proximal lead from the extension connection, cerebrospinal fluid egress through fine gaps between the metallic electrode contacts, and electrode spacing was observed. Patient eventually had centromedian nucleus DBS insertion.

Study 13 Penn D (2012)

Details

Study type	**Case report**
Country	USA
Recruitment period	Not reported
Study population and number	**n=1**
Age and sex	21 years; female
Patient selection criteria	Not applicable
Technique	Bilateral ANT-DBS implantation as per SANTE trial technique (see Fisher R (2010) for more details)
Follow-up	**4 months**
Conflict of interest/source of funding	3 of the authors were contracted by Medtronic to conduct SANTE trial. One of the 3 authors is also a consultant for St. Jude, Non Linear Technologies Spine and Medtronic and stockholder of Intelect Medical, Inc.

Twiddler's syndrome

The patient was enrolled in the SANTE trial and had bilateral ANT-DBS implant. She was presented with recurrent seizures from failure of her DBS stimulator, 6 months after implantation. Radiographic imaging showed the Implantable Pulse Generators (IPG) had been twisted upon itself causing coiling and looping of extension wires. The patient denied any conscious manipulation of the system. Surgical revision was performed, and the desired stimulation effect was achieved. However, patient developed infection at the extension site, the device was removed at fourth month.

Study 14 Doležalová I (2019)

Details

Study type	**Case report**
Country	Czech Republic
Recruitment period	Not reported
Study population and number	**n=1**
Age and sex	41 years; female
Patient selection criteria	Not applicable
Technique	Bilateral ANT-DBS implantation. Stimulation parameters were as follows: amplitude 2.5 V, stimulation frequency 140 Hz, pulse width 90 ms, 5-minute off-time, 1-minute on-time.
Follow-up	**7 years**
Conflict of interest/source of funding	Neither of the authors had any conflict of interest to disclose.

Persistent psychiatric side effects following discontinuation of DBS

The patient with drug-resistant epilepsy was treated with bilateral deep brain stimulation of the anterior nucleus of the thalamus (ANT-DBS). The patient did not note a decrease in seizure frequency, but she did report reduction in seizure severity and duration. The patient developed psychiatric side effects (PSEs), namely irritability, hostility, aggressiveness, and paranoia, after implantation and stimulation initiation. The stimulation was discontinued, and the PSEs were mitigated with medications, but the patient did not return to her pre-implantation state, as documented by repeated psychiatric reports and hospitalizations over the next 7 years. .

Validity and generalisability of the studies

- The patient populations were heterogeneous and included patients with different types of epilepsy and seizures (simple partial, complex partial and generalised tonic–clonic seizures), both between and within studies. 1 RCT included patients with medically refractory partial seizures, including secondarily generalized seizures[1].
- Different studies involved stimulation of different parts of the brain. 2 RCTs and 1 case series involved bilateral implantation of electrodes into the anterior nucleus of the thalamus[1,3,9]. 1 Non-randomized comparative study and 2 small studies from the Cohcrane review involved implantation of electrodes into the centromedian thalamic nucleus[6,8]. 1 RCT and 4 small studies from the Cochrane review involved implanting electrodes into the hippocampus[4,6]. 1 study included in the Cochrane review had DBS implanted in the nucleus accumbens[6].
- The type of stimulation and parameters used varied between studies. Three studies used continuous stimulation[4,9,8] , and 2 RCTs used cyclic stimulation[1,3].
- There may be a lesional effect of electrode placement in addition to the effect of stimulation. In 1 study, 2 patients were seizure free immediately after implantation without stimulation, lasting for at least 12 months[8].
- Apart from the SANTE trial, the other RCTs (including RCTs in the Cochrane review) have very small sample sizes and short-term follow-ups.
- No studies were identified that directly compares DBS with other neurostimulations or surgical interventions.

Existing assessments of this procedure

NHS England Specialised Commissioning Team has published a clinical commissioning policy on deep brain stimulation for refractory epilepsy (all ages) in 2018. Evidence review for the policy document included 1 Cochrane systematic review of DBS for epilepsy which includes the SANTE trial (See Fisher R (2010)). The evidence review reported that no studies were found that

directly compared DBS with other neurostimulation methods like Vagus Nerve Stimulation (VNS) or NeuroPase. The policy statement concluded that there is not enough evidence to support the routine commissioning of deep brain stimulation for refractory epilepsy.

A health technology assessment series by Health Quality Ontario, an arms-length agency of the Ontario government in Canada, conducted an evidence-based analysis of electrical stimulation for drug-resistant epilepsy in 2013. It evaluated the effectiveness of deep brain stimulation (DBS) and vagus nerve stimulation (VNS) for the treatment of drug-resistant epilepsy in adults and children. It identified only one RCT for the DBS, which is included in this overview (Fisher R (2010)). It reported that although DBS is effective at reducing the frequency of seizures in adults, the evidence on this procedure is limited to 1 RCT with substantial limitations; and no studies of DBS with children were identified[15].

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Deep brain stimulation for refractory chronic pain syndromes (excluding headache). NICE interventional procedures guidance 382 (2011). Available from https://www.nice.org.uk/Guidance/IPG382
- Deep brain stimulation for intractable trigeminal autonomic cephalalgias. NICE interventional procedures guidance 381 (2011). Available from https://www.nice.org.uk/Guidance/IPG381
- Deep brain stimulation for tremor and dystonia (excluding Parkinson's disease). NICE interventional procedures guidance 188 (2006). Available from https://www.nice.org.uk/Guidance/IPG188
- Vagus nerve stimulation for refractory epilepsy in children. NICE interventional procedures guidance 50 (2004). Available from https://www.nice.org.uk/Guidance/IPG50
- Deep brain stimulation for Parkinson's disease. Interventional procedures guidance. NICE interventional procedures guidance 19 (2003). Available from http://www.nice.org.uk/guidance IPG19

NICE guidelines

- Epilepsies: diagnosis and management. NICE clinical guideline 137 (Published: 2012, Last update: 2019). Available from https://www.nice.org.uk/guidance/cg137

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Professional expert questionnaires for DBS for epilepsy were submitted and can be found on the NICE website .

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 1 company who manufacture a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- The U.S Food and Drug administration (FDA) has approved the Medtronic DBS therapy for expanding the indications to include Epilepsy on 27 April 2018. It stated in the approval letter that the Medtronic DBS System for Epilepsy has demonstrated safety and effectiveness in patients who averaged

six or more seizures per month over the three most recent months prior to implant of the DBS system (with no more than 30 days between seizures). It was also reported that the Medtronic DBS System for Epilepsy has not been evaluated in patients with less frequent seizures.

- The Medtronic® DBS system for Epilepsy is indicated as adjunctive therapy for the treatment of refractory epilepsy in adults. Although, some studies with children population are included in this overview, the CE Mark certificate for the device is only indicated for individuals 18 years of age or older.

- Ongoing trials

  - Medtronic Deep Brain Stimulation (DBS) Therapy for Epilepsy Post-Approval Study (EPAS) (USA); NCT03900468; Open label study; estimated enrolment: 216; Estimated study start date: October 2019; estimated study completion date: March 2027.

  - Deep Brain Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (FRANCE); NCT02076698; RCT; estimated enrolment:62; Study start date: June 2014; estimated study completion December 2019.

  - Product Surveillance Registry- Deep Brain Stimulation for Epilepsy (MORE) (Multicentre); NCT01521754;Observational study; Actual enrolment: 191; Actual study start date: March 2012; Actual primary completion date: June 2019.

References

1. Fisher R, Salanova V, Witt T et al. (2010) Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 51: 899–908.
2. Salanova V, Witt T, Worth R et al. (2015) Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy. Neurology, 84(10), pp.1017-1025.
3. Herrman H, Egge A, Konglund A et al. (2018) Anterior thalamic deep brain stimulation in refractory epilepsy: A randomized, double-blinded study. Acta Neurologica Scandinavica.
4. Cukiert A, Cukiert C, Burattini J et al. (2017) Seizure outcome after hippocampal deep brain stimulation in patients with refractory temporal lobe epilepsy: A prospective, controlled, randomized, double-blind study. Epilepsia, 58(10), pp.1728-1733.
5. Chang B. and Xu J. (2017) Deep brain stimulation for refractory temporal lobe epilepsy: a systematic review and meta-analysis with an emphasis on alleviation of seizure frequency outcome. Child's Nervous System, 34(2), pp.321-327.
6. Sprengers M, Vonck K, Carrette E et al. (2017) Deep brain and cortical stimulation for epilepsy. Cochrane Database of Systematic Reviews.
7. Yan H, Toyota E, Anderson M et al. (2019) A systematic review of deep brain stimulation for the treatment of drug-resistant epilepsy in childhood. Journal of Neurosurgery: Pediatrics, 23(3), pp.274-284.
8. Valentín A, García Navarrete E, Chelvarajah Ret al. (2013). Deep brain stimulation of the centromedian thalamic nucleus for the treatment of generalized and frontal epilepsies. Epilepsia, 54(10), pp.1823-1833.
9. Kim S, Lim S, Kim J et al. (2017) Long-term follow-up of anterior thalamic deep brain stimulation in epilepsy: A 11-year, single center experience. Seizure, 52, pp.154-161.
10. Tröster A, Meador K, Irwin C, Fisher R (2017) Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy. Seizure, 45, pp.133-141.
11. Hamdi H, Robin E, Stahl J et al. (2019) Anterior Thalamic Stimulation Induced Relapsing Encephalitis. Stereotactic and Functional Neurosurgery, 97(2), pp.132-136.
12. Son, B., Choi, J. and Ha, S. (2018) Cerebrospinal fluid egress from the quadripolar deep brain stimulation electrode for anterior nucleus of the

thalamus for refractory epilepsy. Asian Journal of Neurosurgery, 13(2), p.407.

13. Penn D, Wu C, Skidmore C et al. (2012) Twiddler's syndrome in a patient with epilepsy treated with deep brain stimulation. Epilepsia, 53(7), pp.e119-e121.
14. Doležalová I, Kunst J, Kojan M et al. (2019) Anterior thalamic deep brain stimulation in epilepsy and persistent psychiatric side effects following discontinuation. Epilepsy Behav Rep;12:100344.
15. Chambers A, Bowen J.M, (2013). Electrical stimulation for drug-resistant epilepsy: an evidence-based analysis. Ontario health technology assessment series, 13(18), 1–37.

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	23/01/2020	Issue 1 of 12, January 2020
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	23/01/2020	Issue 1 of 12, January 2020
HTA database (CRD website)	-	-
MEDLINE (Ovid)	23/01/2020	1946 to January 22, 2020
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	23/01/2020	1946 to January 22, 2020
EMBASE (Ovid)	23/01/2020	1974 to January 22, 2020

Trial sources searched

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Deep Brain Stimulation/
2	((deep or electric*) adj4 brain* adj4 stimul*).tw.
3	(dbs or dbs-stn).tw.
4	or/1-3
5	Electric Stimulation Therapy/
6	(electric* adj4 stimul* adj4 (therap* or treat*)).tw.
7	or/5-6
8	exp Brain/
9	brain*.tw.
10	or/8-9
11	7 and 10
12	4 or 11
13	exp epilepsy/
14	(epileps* or epilept* or aura* or seizure*).tw.
15	(electric* adj4 hyperactiv*).tw.
16	or/13-15
17	12 and 16
18	dbs therapy.tw.
19	activa.tw.
20	18 or 19
21	16 and 20
22	17 or 21
23	Animals/ not Humans/
24	22 not 23
24	limit 24 to ed=20110901-20200131

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Case series with fewer than 10 patients have been excluded. Case reports have been excluded unless they describe a safety event.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Anderson D, Németh A, Fawcett K et al. (2017). Deep Brain Stimulation in Three Related Cases of North Sea Progressive Myoclonic Epilepsy from South Africa. Movement Disorders Clinical Practice, 4(2), 249–253.	Case series n=3	Review of cases with previous DBS of the caudal Zona for North Sea Progressive Myoclonic Epilepsy. Showed there was a reduction in GTC seizures in all cases, and two patients exhibited a reduction in involuntary movements, as evaluated during long-term follow-up.	Larger studies are included.
Boon P, De Cock E, Mertens A et al. (2018). Neurostimulation for drug-resistant epilepsy: A systematic review of clinical evidence for efficacy, safety, contraindications and predictors for response. Current Opinion in Neurology.	Systematic review of all neurostimulation types	Low-to-moderate quality evidence supported the efficacy and safety of VNS, DBS and RNS in patients with drug-resistant epilepsy.	The studies included in this systematic review are already included in in Table 2.
Bouwens van der Vlis T, Schijns O, Schaper F et al. (2019). Deep brain stimulation of the anterior nucleus of the thalamus for drug-resistant epilepsy. Neurosurgical Review. Springer Verlag.	Review	ANT-DBS for drug-resistant epilepsy is a safe and well-tolerated therapy, where particular emphasis must be given to monitoring of depression and memory function. ANT-DBS is an efficacious treatment modality, even when curative procedures or lesser invasive neuromodulative techniques failed.	Review
Boviatsis E, Stavrinou L, Themistocleous M et al. (2010). Surgical and hardware complications of deep brain stimulation. A seven-year experience and	Case series n=106 (only 1 patient is epilepsy patient) FU= not reported	Serious complications with permanent sequelae are rare and in—many cases—dependent on the surgeon's experience. For all	Safety events arising from DBS for epilepsy are already described.

review of the literature. Acta Neurochirurgica, 152(12), 2053–2062.	Included other conditions such as Parkinson's disease, dystonia, tremor, OCD, central pain syndrome.	conditions, there were 12 procedure related complications which included death (n=1) aborted procedure (n=1), respiratory distress (n=3), intracranial haemorrhage (n=2), epilepsy (n=1) , post-operative confusion or agitation (n=3) and malignant neuroleptic syndrome (n=1). (It is not reported which of these complications are experienced by the epileptic patient)	
Chan A, Rolston J, Rao V et al. (2018). Effect of neurostimulation on cognition and mood in refractory epilepsy. Epilepsia Open. Wiley-Blackwell Publishing Ltd.	Review Reviews all neuromodulation including invasive and non-invasive techniques.	Overall, current evidence indicates that the neurostimulation therapies do not produce deterioration in cognition or mood, and there is some evidence that cognition and mood may improve with some invasive forms of neurostimulation. However, the available evidence was generally limited to studies with small sample sizes or methodology susceptible to confounding.	Review
Choi J, Lee S, Shon Y et al. (2015). Long-Term Migration of a Deep Brain Stimulation (DBS) Lead in the Third Ventricle Caused by Cerebral Atrophy in a Patient with Anterior Thalamic Nucleus DBS. Journal of Epilepsy Research, 5(2).	Case report n=1	**Lead Migration** A case of re-implantation of DBS lead in the left ANT because of lead migration into the third ventricle detected 8 years after the first DBS, and which was caused by the significant enlargement of the lateral and third ventricles. Post-operatively, chronic stimulation was provided with improved epileptic seizure frequency.	Safety event (Neurostimulator migration) already described.
Cox J, Seri S, & Cavanna A (2014). Clinical utility of implantable neurostimulation devices as adjunctive treatment of uncontrolled seizures. Neuropsychiatric Disease and Treatment.	Review Review article including all neuromodulation types.	Implantable neurostimulation devices, including VNS, DBS, and RNS, appear to be a safe and beneficial	The studies for DBS are included either in the Cochrane review or separately as RCT.

		treatment option for patients with refractory epilepsy.	
Cukiert A, Cukiert C, Burattini J et al. (2015). Seizure Outcome After Battery Depletion in Epileptic Patients Submitted to Deep Brain Stimulation. Neuromodulation: Technology at the Neural Interface, 18(6), pp.439-441.	Case series n=9 FU= 6 months	9 patients who had battery depletion after at least 3 years of DBS were studied. 2 patients did not have any changes in seizure frequency after battery depletion. 7 patients had their seizure frequency increase.	Post-battery depletion seizure frequency study. Not relevant.
Degiorgio C, & Krahl, S (n.d.). Neurostimulation for Drug-Resistant Epilepsy.	Review article	Reviews all neurostimulation options including DBS. In a phase III randomized controlled trial of DBS of the anterior thalamus, the active-treatment group experienced a 38.8% reduction in seizures versus 22.8% in the control group.	Review article. The RCT it reviewed for DBS is already included in table 2.
Gooneratne I, Green A, Dugan P et al. (2016). Comparing neurostimulation technologies in refractory focal-onset epilepsy Journal of Neurology, Neurosurgery & Psychiatry;87:1174-1182.	Review	The study compared long-term (5-year) outcomes of newer neurostimulation techniques (DBS and responsive neurostimulations) with the more established Vagal nerve stimulation (VNS). It identified 1 study for DBS, 1 study for CRS and 4 studies for VNS. All neurostimulation technologies showed long-term efficacy, with progressively better seizure control over time. Sustained improvement in quality of life measures was demonstrated in all modalities. Intracranial neurostimulation had a greater side effect profile compared with extracranial stimulation, though all forms of stimulation are safe.	Review article
Hachem L, Yan H and Ibrahim G (2018). Invasive Neuromodulation for the Treatment of Pediatric	Review	Reviews all neurostimulation techniques including DBS for children. The	Review

Epilepsy. Neurotherapeutics, 16(1), pp.128-133.		review stated that there is lack of long-term evidence of chronic brain stimulation in children and with continued brain development with age, it remains unknow whether electrode or wire migration may occur and compromise treatment effect or lead to complications. Children may be more susceptible to infection.	
Han C, Hu W, Stead M et al (2014). Electrical stimulation of hippocampus for the treatment of refractory temporal lobe epilepsy. Brain Research Bulletin, 109, pp.13-21.	Review	Review of the literature for electrical stimulation of hippocampus for refractory epilepsy. Animal and clinical studies have demonstrated that electrical stimulation is an effective and safe treatment. Successful application of responsive neurostimulation system in the treatment of temporal love epilepsy has also been reported.	Review
Hartikainen K, Sun L, Polvivaara M et al. (2014). Immediate effects of deep brain stimulation of anterior thalamic nuclei on executive functions and emotion-attention interaction in humans. Journal of Clinical and Experimental Neuropsychology, 36(5), 540–550.	Case series n=12	ANT–DBS increased the amount of commission errors—that is, errors where subjects failed to withhold from responding. The results highlight the need to consider affective and cognitive side-effects in addition to the therapeutic effect when adjusting stimulation parameters.	Neurocognitive outcomes are described in Table 2 studies.
Järvenpää S, Peltola J, Rainesalo S et al. (2018). Reversible psychiatric adverse effects related to deep brain stimulation of the anterior thalamus in patients with refractory epilepsy. Epilepsy and Behavior, 88, 373–379.	Case series n=22 FU= 1 year	At the group level, no changes on mood were observed during ANT DBS treatment. Two patients with former histories of depression experienced sudden depressive symptoms related to DBS programming settings; these were quickly alleviated after changing the stimulation parameters. In addition, two patients with no	Larger study with neuropsychological outcomes is included.

		previous histories of psychosis gradually developed clear paranoid and anxiety symptoms that also relieved slowly after changing the programming settings.	
Järvenpää S, Rosti-Otajärvi E, Rainesalo S et al. (2018). Executive functions may predict outcome in deep brain stimulation of anterior nucleus of thalamus for treatment of refractory epilepsy. Frontiers in Neurology.	Case series (retrospective study) n= 16 FU= > 2 years	Non-responders performed worse than responders in neuropsychological tasks measuring executive functions and attention, such as the Trail-Making Test. Better executive functions and attention seemed to predict improved clinical outcome after the ANT DBS surgery.	Larger studies are included.
Jitkritsadakul O, Bhidayasiri R, Kalia S, Hodaie M et al. (2017). Systematic review of hardware-related complications of Deep Brain Stimulation: Do new indications pose an increased risk?. Brain Stimulation, 10(5), pp.967-976.	Systematic review n=139 (for epilepsy)	Systematic review of hardware-related complications of DBS for all indications. The most common hardware-related complications are infection, lead migration, fracture or failure of the lead or other parts of the implant, IPG malfunction, Skin erosion.	The studies for DBS in this review are included in Table 2, either in the Cochrane review or separately.
Klinger N. and Mittal, S (2016). Clinical efficacy of deep brain stimulation for the treatment of medically refractory epilepsy. Clinical Neurology and Neurosurgery, 140, pp.11-25.	Review	The utility of DBS in the treatment of epilepsy can be seen with decreases in seizure frequency, severity, complications related to falls, cognitive function and medication tapering/discontinuation. Some patients treated with DBS achieve complete seizure freedom. Both mortality and quality of life may be positively affected by DBS.	Review
Klinger N, & Mittal S (2018). Deep brain stimulation for seizure control in drug-resistant epilepsy. Neurosurgical Focus, 45(2).	Review	Deep brain stimulation is a safe and efficacious treatment for drug-resistant epilepsy. It is effective in reducing seizure frequency in patients who otherwise have no other treatment options. Some patients treated with DBS can attain seizure freedom.	Review

Kowski A, Voges J, Heinze H et al. (2015). Nucleus accumbens stimulation in partial epilepsy - A randomized controlled case series. Epilepsia, 56(6), e78–e82.	Randomized controlled case series n=4 FU= 12 months	Nucleus accumbens stimulation in 4 patients with partial epilepsy showed that three patients had ≥50% reduction in frequency of disabling seizures without further improvement with additional anterior thalamic nucleus stimulation. Patient-reported outcome and neurocognitive testing remained unchanged.	Included in the Cochrane review of table 2.
Krishna V, King N, Sammartino F et al. (2016). Anterior nucleus deep brain stimulation for refractory epilepsy: Insights into patterns of seizure control and efficacious target. Neurosurgery, 78(6), 802–811.	Case series (retrospective) n=16 Mena FU= 4.3 years	11 out of 16 patients reported .50% decrease in seizure frequency with long-term stimulation. 56% (9/16) of patients showed insertional effect with duration varied from 2 to 4 months.	Larger studies are included.
Kulju T, Haapasalo J, Lehtimäki K et al. (2018). Similarities between the responses to ANT-DBS and prior VNS in refractory epilepsy. Brain and Behavior, 8(6).	Case series n=11 FU= 10 years	A total of 11 patients with previous VNS therapy underwent ANT-DBS implantation. in 10 of 11 patients, the response to VNS seemed to be similar to the response to DBS therapy. Progressive response to VNS was likely to correlate with a progressive response to DBS in three of three patients. Partial response to VNS was associated with a fluctuating response pattern to DBS in two patients. Five of six non-responders to VNS were also non-responders to DBS.	The study investigated the potential correlation between therapeutic responses to VNS and ANT-DBS, and therefore, only included patients with prior VNS therapy.
Kwon C, Ripa V, Al-Awar O et al. (2018). Epilepsy and neuromodulation—Randomized controlled trials. Brain Sciences, 8(4).	Review article	Reviews RCTs for all neuromodulation options for epilepsy. Although reductions in epilepsy frequency and focus firing are common in the trials for neuromodulations for epilepsy, obtaining seizure freedom is rare. Further investigations	Review

		are necessary to delineate effective targeting, minimize side effects that are related to chronic implantation and to improve the cost effectiveness of these devices.	
Lee K, Shon Y & Cho C (2012). Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy. Stereotactic and Functional Neurosurgery, 90(6), 379–385.	Case series n=15 Median FU = 39 months	The study showed a statistically significant decrease in the seizure frequency, with a mean reduction of 70.4%.	Larger studies are included.
Lehtimäki K, Möttönen T, Järventausta K et al. (2016). Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy. Brain Stimulation, 9(2), 268–275.	Case series n=15 FU= 5 years	The study investigated correlation between the stimulation site and outcome. Contacts in successful treatment trials were located significantly more anterior and superior both in AC–PC and ANT-normalized coordinate systems. The anti-epileptic effect of anterior thalamic DBS may be dependent on stimulation site specially in the anterior to posterior axis.	This is analysis of contact locations in anterior thalamic region. Larger studies for ANT stimulation are included in Table 2.
Li M & Cook M (2018). Deep brain stimulation for drug-resistant epilepsy. Epilepsia, 59(2), 273–290.	Review	Stimulation of the anterior nucleus of the thalamus (ANT) and hippocampus (HC) has been shown to decrease the frequency of refractory seizures. Half of all patients from clinical studies experienced a 46%-90% seizure reduction with ANT-DBS, and a 48%-95% seizure reduction with HC-DBS. The efficacy of stimulating other targets remains inconclusive due to lack of evidence.	Review. A Cochrane review and systematic review with the same studies are included in Table 2.
Miatton M, Van Roost D, Thiery E et al. (2011). The cognitive effects of amygdalohippocampal deep brain stimulation in patients with temporal lobe epilepsy. Epilepsy & Behavior, 22(4), pp.759-764.	Case series n=10 FU= 6months The study looked at cognitive effects of amygdalohippocampal	Group analyses revealed no overall pattern of change in cognitive measures, but improvement was seen in emotional well-being. Individual results varied over a broad spectrum	Larger studies with neurocognitive outcomes are included.

	deep brain stimulation.	ranging from no cognitive effects to negative effects on intelligence capacities, divided attention, and concept formation, to positive effects on speed of information processing and speed of finger movements.	
Morace R, Gennaro G & De Risi M. (2016). Deep brain stimulation for intractabile epilepsy Outocm predictors in epilepsy surgery View project Sellar barrier View project. Article in Journal of neurosurgical sciences.	Review	Among the different targets and stimulation types, only ANT stimulation and Responsive nerve stimulation have achieved class I evidence of efficacy. Other targets such as hippocampus and centromedian nucleus stimulation also reduce seizure frequency in epilepsy but they were small sample size studies.	Review
Nagel S & Najm I (2009) Deep Brain Stimulation for Epilepsy. *Neuromodulation: Technology At The Neural Interface*, *12*(4), 270-280	Review	A number of studies in animals and humans indicate that electrical stimulation may be an alternative treatment for some patients with medically intractable epilepsy who are not candidates for conventional surgical options. The reduction in the number and/or severity of seizures found in some studies supports further investigation into the effects of electrical stimulation on the brain and the continuation of testing in animals and humans.	Review article
Nora T, Heinonen H, Tenhunen M et al. (2018). Stimulation induced electrographic seizures in deep brain stimulation of the anterior nucleus of the thalamus do not preclude a subsequent favorable	Case report n=1	**Stimulation induced seizures** Patient developed visual symptoms and atypical seizures with the onset of ANT-DBS therapy for refractory epilepsy. Lowering the stimulation	Safety event (new seizure) described in table 2.

treatment response. Frontiers in Neurology.		voltage alleviated these symptoms.	
Novais F, Pestana L, Loureiro S et al. (2019) Predicting de novo psychopathology after epilepsy surgery: A 3-year cohort study. *Epilepsy & Behavior*, *90*, 204-208	Case series n=106 Patients with refractory epilepsy who had epilepsy surgery (either resective surgery or ANT-DBS)	15% (16/106) developed psychiatric disorders that were never identified before surgery. Multilobar epileptogenic zone ($p = 0.001$) and DBS of the ANT-DBS ($p = 0.003$) were found to be significant predictors of these events. People with more generalized epileptogenic activity and those who undergo ANT-DBS seem to present an increased susceptibility for the development of mental disorders, after neurosurgical interventions, for the treatment of refractory epilepsy.	Safety events already described
Novais F, Pestana L, Loureiro S et al. (2019). Predicting de novo psychopathology after epilepsy surgery: A 3-year cohort study. Epilepsy & Behavior, 90, pp.204-208.	Cohort study n= 106 (99 Resective surgery vs 7 DBS) FU= 3 years	Multilobar epileptogenic zone, bilateral epileptogenic zone, ANT-DBS, and higher Engel class were found to significant predictors of *de novo* major psychopathology.	This study has only 7 patients with DBS for epilepsy. Larger studies with neurocognitive outcomes are included.
Oh Y, Kim H, Lee K et al. (2012). Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients. Seizure, 21(3), 183–187.	Case series n=9 FU= > 1 year	This study investigated the cognitive outcomes at least 12 months after DBS to the bilateral anterior thalamic nucleus (ATN). Cognitive testing showed favourable results for verbal fluency tasks (letter and category, $p < 0.05$), and a significant improvement in delayed verbal memory was observed ($p = 0.017$). No significant changes in general abilities (IQ, MMSE), information processing or executive function.	Larger studies with neurocognitive outcomes are included.
Papageorgiou P, Deschner J and Papageorgiou S. (2016). Effectiveness and Adverse Effects of Deep Brain Stimulation: Umbrella Review of Meta-Analyses. Journal of	Umbrella review of meta-analysis n= 1 study for epilepsy	Reviews meta-analysis of DBS for all indications. Although DBS has emerged as a viable surgical intervention to treat various disabling	1 of the 2 studies from this umbrella review is included in Table 2 and another 1 is discussed in

Neurological Surgery Part A: Central European Neurosurgery, 78(02), pp.180-190.		neurologic symptoms, existing studies fail to adequately support its use based on robust evidence without hints of bias.	Existing Assessments of the Procedure section.
Park H, Choi S, Joo E et al. (2019) The Role of Anterior Thalamic Deep Brain Stimulation as an Alternative Therapy in Patients with Previously Failed Vagus Nerve Stimulation for Refractory Epilepsy. Stereotact Funct Neurosurg; 97:176-182	Case series n=7 Patients with refractory epilepsy with previously failed VNS	Five (71.3%) of the 7 patients experienced a >50% reduction of seizure counts after DBS; 1 responder reached a seizure-free status after DBS therapy. Favourable outcomes of ANT-DBS surgery were observed in individual patients with refractory epilepsy who had not responded to prior VNS	Small case series. Patients with previous VNS failure.
Rolston J, Englot D, Wang D et al. (2012). Comparison of seizure control outcomes and the safety of vagus nerve, thalamic deep brain, and responsive neurostimulation: Evidence from randomized controlled trials. Neurosurgical Focus, 32(3).	Review	Compares published efficacy and safety results from RNS trial, VNS trial and ANT-DBS trial. All 3 trials are stimulation-based neuromodulation therapies for epilepsy with positive Class I evidence. There are no head-to head comparisons of these therapies, but all appear to have some limited effectiveness, and all might have application for particular subgroups of patients.	Review
Schulze-Bonhage A. (2019). Long-term outcome in neurostimulation of epilepsy. Epilepsy & Behavior, 91, pp.25-29.	Review	Outcome data of neurostimulation (including DBS, RNS and VNS) showed that it is an effective, yet palliative approach. More than half of the patients benefit from this, yet only 5-23% of patients achieved seizure-free periods, clearly inferior to the efficacy of epilepsy surgery.	Review
Sitnikov A, Grigoryan Y, & Mishnyakova L (2018). Bilateral stereotactic lesions and chronic stimulation of the anterior thalamic nuclei for treatment of	Case series n=12 (DBS only) FU= 12 months	ANT DBS was performed in 12 patients. Mean seizures reduction reached 80.3% in group of patients with ANT DBS with two non-	Larger studies for ANT-DBS are included.

pharmacoresistant epilepsy. Surgical Neurology International, 9(1).		responders. The study also involved 19 patients with stereotactic radiofrequency lesions of ANT, and it found that mean seizure reduction in this group was 91.2%.	
Son B, Shon Y, Choi J et al. (2016). Clinical Outcome of Patients with Deep Brain Stimulation of the Centromedian Thalamic Nucleus for Refractory Epilepsy and Location of the Active Contacts. Stereotactic and Functional Neurosurgery, 94(3), pp.187-197.	Case series n=14 Mean FU=18.2 months	The mean percent seizure reduction was 68%. 78.6% (11/14) achieved >50% improvement in seizure frequency. The location of chronic contacts in chronic stimulation of centromedian thalamic did not influence the outcome of seizure reduction. The locations of active contacts used in multilobar epilepsy were identified as being more dorsal to those used in generalised epilepsy.	Larger studies are included.
Son B-C, Shon Y-M, Kim S et al. (n.d.). Technical Implications in Revision Surgery for Deep Brain Stimulation (DBS) of the Thalamus for Refractory Epilepsy. Original Article Journal of Epilepsy Research.	Case series n=23	Misplacement of the electrode occurred in 1 (25%) of 4 ANT DBS and 2 (14.3%) of 14 patients with centromedian thalamic DBS. For verification of the location of lead placement, magnetic resonance imaging (MRI) was superior to computed tomography and EEG.	Safety event (revision due to malposition) already described.
Velasco A, Velasco F, Jiménez F et al. (2006), Neuromodulation of the Centromedian Thalamic Nuclei in the Treatment of Generalized Seizures and the Improvement of the Quality of Life in Patients with Lennox–Gastaut Syndrome. Epilepsia, 47: 1203-1212	Case series n=13 FU= 18 months	Patients with Lennox–Gastaut syndrome (LGS) received DBS stimulation in centromedian thalamic nucleus. Overall seizure reduction was 80%. The three patients with poorest outcomes for seizure control did not improve their ability scale score. In contrast, the two patients rendered seizure free are living a normal life at present. The remaining eight patients experienced progressive improvement, from being totally disabled to becoming independent in	Patients with Lennox–Gastaut Syndrome (Childhood epilepsy).

		five cases and partially dependent in two.	
Voges B, Schmitt F, Hamel W et al. (2015). Deep brain stimulation of anterior nucleus thalami disrupts sleep in epilepsy patients. Epilepsia, 56(8), e99–e103.	Case series n=9 FU= 1 to 21 months	ANT-DBS interrupts sleep in a voltage-dependent manner and reduction of nocturnal DBS voltage seems to lead to improvement without hampering efficacy of ANT-DBS.	Safety event (sleep disturbance) already described in other studies in Table 2.
Vonck K, Sprengers M, Carrette E et al. (2013). A decade of experience with deep brain stimulation for patients with refractory medial temporal lobe epilepsy. International Journal of Neural Systems, 23(1).	Case series n=11 Mean FU= 8.5 years	11 patients with refractory medial temporal lobe (MTL) epilepsy underwent MTL DBS. When unilateral DBS failed to decrease seizures by >90%, a switch to bilateral MTL DBS was proposed. After a mean follow-up of 8.5 years (range: 67–120 months), 6/11 patients had a ≥ 90% seizure frequency reduction with 3/6 seizure-free for >3 years.	Larger studies are included.
Wong S, Mani R, Danish S. (2019) Comparison and Selection of Current Implantable Anti-Epileptic Devices. Neurotherapeutics.;16(2):369-380.	Review	The review compared three implantable anti-epileptic devices (DBS, VNS and RNS). Overall, efficacy appears to be similar between DBS and RNS, with a slight long-term performance edge for DBS. VNS performance trails somewhat. Head-to-head trials addressing efficacy and tolerability would be ideal for a more direct comparison between competing technologies.	Review article
Yan G,Wei H, Chong L et al. (2013). Brain stimulation for treatment of refractory epilepsy. Chinese Medical Journal.	Review	Reviews DBS and responsive neuro stimulation for refractory epilepsy. Although statistically significant reductions in seizures have been observed using several different stimulation techniques, including VNS, DBS, and RNS, these effects are currently only palliative and do not approach the efficacy comparable with	Review

		that seen in resection in appropriately selected patients.	
Zangiabadi N, Ladino L, Sina, F et al. (2019) Deep Brain Stimulation and Drug-Resistant Epilepsy: A Review of the Literature. *Frontiers In Neurology*, *10*	Review	Deep brain stimulation for seizures may be an option in patients with drug-resistant epilepsy. Anterior thalamic nucleus stimulation could be recommended over other targets	Review article
Zhou J, Chen T, Harrison Farber S et al. (2018). Open-loop deep brain stimulation for the treatment of epilepsy: A systematic review of clinical outcomes over the past decade (2008-present). Neurosurgical Focus, 45(2).	Systematic Review (no meta-analysis)	Level I evidence supports the safety and efficacy of stimulating the anterior nucleus of the thalamus and the hippocampus for the treatment of medically refractory epilepsy. Level III and IV evidence supports stimulation of other targets for epilepsy.	Review.