

NHS England

Evidence review: Deep brain stimulation in the treatment of severe, medication refractory Tourette syndrome

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Commissioning

Draft for consultation

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1. Introduction

Tourette syndrome (TS), a non-movement disorder, is defined as the presence of multiple motor and vocal tics, starting in childhood and persisting for more than one year. It has a prevalence of about 1%, and is slightly more common in males. Symptoms tend to improve, but not disappear, as children reach adulthood. Some patients presenting with a tic disorder for the first time in adulthood have, in retrospect, a history of subtle undiagnosed tics or obsessive compulsive behaviours in childhood and are likely part of the same spectrum as childhood onset TS. Rarely, tic like movements can occur for the first time in adulthood secondary to medications, structural lesions, infections or neurodegeneration and should be considered separately from patients with Tourette syndrome.

A small group of TS patients have severe and disabling tics (extreme movements and non-suppressible noises) that persist despite attempts at conventional treatment strategies and urgently require further treatment options. These patients are at high risk of developing additional physical problems as a result of violent tics e.g. spinal cord injuries due to severe whiplash-like motor tics, self-injurious behaviours, depression, deliberate self harm, and are at high risk of suicide. The presence of frequent, severe and obvious motor and vocal tics is often socially unacceptable and prevents education, work, and establishing or maintaining friendships and family relationships. Individuals who are able to, or are forced to, leave the parental home often require specialist housing requirements such as soundproofing or structural reinforcements to prevent damage to property occurring secondary to violent motor tics.

Deep brain stimulation (DBS) is a neurosurgical intervention for the management of severe movement and non-movement disorders in patients who: have not responded to recommended first line treatments, have suffered severe side-effects to treatment or who have experienced wide fluctuations in response to drugs (on-off syndrome). The pathophysiology of TS is thought to result from a defect in the cortical-basal ganglia–thalamo–cortical neuronal circuit, hence this has been the target of modulation of DBS for the control of tics. (Cannon E *et al* 2012). DBS involves the implantation of leads with electrodes into one of three areas in the brain, the thalamus, globus pallidus (GP) or subthalamic nucleus. The leads are connected to extensions tunnelled beneath the skin that connect to a neurostimulator device implanted subcutaneously in the chest or stomach area. It is activated after the wounds from surgery have healed and is adjusted, in parallel with adjusting the dose of medication, over the ensuing weeks and months. Stimulation from the device modifies some of the electrical signals in the brain thereby improving symptoms. The neurostimulator runs on either rechargeable or non-rechargeable batteries, the latter of which typically last between three and five years.

There is increasing evidence that the use of DBS for medication resistant TS is effective at reducing the severity of tics, although the exact site of implantation of electrodes, their safety and long term effectiveness are still unclear. This evidence review (ER) was requested by the Neurosciences CRG (Trauma Programme of Care Board) in order to be able to make evidence-based recommendations to NHS England about whether it should be routinely commissioned in the NHS. The PICO identified the population, intervention, comparator and outcomes to focus on for the evidence review (Appendix 2) and posed two research questions:

“Is DBS clinically effective at improving tic severity in severe medication refractory Tourette patients?”

An important subsequent question is;

“Does DBS lead to improvement in Quality of life in severe medication refractory Tourette patients?”

2. Summary of results

- The eight studies included in this ER showed an improvement in total Yale global tic severity scale (YGTSS) scores, although the degree of improvement varied quite widely. Most of the studies were limited by small sample sizes and this, together with differences in how they were conducted, limits the usefulness of the findings so that we cannot tell with any great degree of certainty, whether DBS would work in the same or similar way in any other patients with severe and difficult to treat TS.
- A number of adverse events (AEs) and side effects were reported from the studies. However, these were mostly incidental findings rather than findings from studies designed specifically to look for them. As such, all we can infer is that symptoms such as lethargy and dizziness may be associated with DBS, but it is by no means certain that any of them will occur or that other AEs and side effects that have not yet been identified might be equally likely to occur.
- The primary research trials included varied in their quality: the numbers of patients varied between 3 and 17, with the systematic review and meta-analysis including 162 and 150 patients respectively. One study only had 1 patient in the comparator arm. (Ackermans et al., 2011) Hence the power of the studies to identify meaningful results was limited and the results presented may have been an over or under-estimate of reality. The patient characteristics were also either unclear or biased (one study had all male patients), baseline medication and changes to medication were not necessarily reported and neither were co-morbidities. The electrodes were also implanted in different locations in the brain. This means that other factors could have influenced the magnitude of the outcome responses, such as the amount of improvement in YGTSS score, apart from the DBS.

3. Methodology

1. Scoping: A PICO form (population, intervention, comparator, outcomes) was prepared by the Clinical and Public Health Leads for this policy area at NHS England (see section 10 below).
2. Appraisal: The literature search was undertaken by the PHE library service, based on the PICO. The following databases/sites were searched for relevant publications: The Cochrane Library, EMBASE, MEDLINE, PSYCINFO, NICE Evidence and the Trip Pro database.
3. The titles and abstracts of the results from the literature searches were examined, both by the reviewer and the appraiser (for quality assurance purposes) using the criteria from the PICO. Where there was disagreement, the reviewer and appraiser discussed the papers and decided on their inclusion or exclusion. Full text versions of papers that were deemed to be useful or potentially useful were obtained and a decision made on the appropriateness of including their findings in this review.
4. Generally, where reasonable or good quality phase 3 studies were available, they were used in preference to earlier phase 1 and 2 studies. No cost-effectiveness analyses were identified.
5. All randomised controlled trials included in this evaluation were assessed as to their quality using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria, as well as the applicability of the results (direct or indirect).
6. The evidence to support individual findings was graded.
7. The appraiser selected some of the papers appraised by the reviewer to check for agreement of interpretation.

4. Results

Twenty nine studies were selected for inclusion (out of a total of 343 identified from the literature review). Some reasons for exclusion of papers included that they were duplicates, included only 1 patient, that they were not in English, were abstracts, the outcome was not one of those recommended in the PICO, or that they appeared to report on the same study population in which case the most recent article was usually selected. Of these 29, 6 were abstracts, 5 were not free to access, 1 was in a Chinese population in China, 1 was incorrectly referenced and was already included, 2 included other psychiatric disorders, not just TS, and the results could not easily be unpicked, 2 included children (≤ 18 years) and 3 case series studies had a study population of 3 patients or fewer. The patient group of one study overlapped with another paper, but was included because it provided information over a longer follow-up period. This left a total of 8 studies that were included in the ER.

Four of the studies were RCTs (2/4 were pilot studies, 1 was an extension of one of the pilot studies), 1 was a systematic review and meta-analysis and the other 2 were a case series of 11 patients and its continuation study, which included an additional 6 patients ($n=17$).

No cost-effectiveness studies were identified.

The results of the papers included are summarised in Table 1, and an overview is presented here. All studies implanted electrodes in the thalamic or Globus Pallidus areas of the brain, although the precise locations differed. Only one study (Okun et al., 2013) used scheduled, rather than continuous, stimulation.

The UK-based RCT by Kefalopoulou *et al* (Kefalopoulou *et al.*, 2015), was based on 13 patients who were randomised to 3 month blocks of ON or OFF DBS followed by an open label phase with continuous stimulation (ON) that lasted for up to 36 months. YGTSS scores improved when ON and OFF stimulation phases were compared (mean 15.9%) as well as continuous ON compared to baseline (mean 22.6%). There was also an overall improvement in GTSQoL (Gilles de la Tourette syndrome quality of life scale) score of 38.9% (95%CI 19.7-58, $p=0.001$) between baseline and the open label phase. The Beck Depression Inventory score improved by 43.2% ($p=0.025$). There were three serious AEs: two patients developed infection of DBS hardware necessitating removal and antibiotics (both were subsequently re-implanted successfully); one required admission to hospital for alteration of stimulation settings and benzodiazepines.

The second RCT (Ackermans et al., 2011) recruited from two sites, one in the Netherlands and one in Belgium. Similar to the Kefalopoulou study, patients were randomised to ON and OFF stimulation followed by continuous stimulation (ON) for six months. Analysis was based on six patients and showed a 37% ($p=0.046$) improvement in YGTSS in the OFF versus ON periods that increased to 49% ($p=0.0028$) at one year open label fup. There was also an improvement in the modified Rush Video Based tic Rating Scale (MRVRS) of 35% ($p=0.046$) compared with the score pre-operatively.

Three patients had AEs related to surgery: one of whom had a small parenchymal haemorrhage resulting in vertical gaze palsy that resolved after six months. One patient developed a staphylococcus aureus infection in the infraclavicular region, which was successfully treated with 6 weeks of intravenous antibiotics. The third patient, who had symptoms of lethargy, binge eating and frequent falls, had developed cerebral atrophy that had not been there previously.

Other side effects included lethargy inhibiting activities of daily living (all patients) and multi-directional nystagmus (one patient).

An RCT pilot study, which took place in Paris, France, included three participants (Welter et

al., 2008). This randomly assigned patients to stimulation of the centromedian-parafascicular complex of the thalamus (CM-pf) or globus pallidus internus (GPI) electrodes or both, and undertook open long-term follow-up (fup). YGTSS scores improved, compared to pre-operative assessment between 65%-96% for GPI, 30%-64% for CM-pf and 43%-76% for both. No adverse events were observed in the fup period of up to 60 months.

A systematic review (57 studies; 162 patients) and meta-analysis (48 studies; 150 patients) conducted by Baldermann *et al* showed a median improvement in YGTSS scores of 52.68% (n=156; IQR 40.83; p<0.001) between baseline and last reported fup (Baldermann *et al.*, 2016). The majority of the decrease occurred in the first post-operative months. There was also a median improvement in MRVRS scores of 48% (n=27; IQR=11.73; p<0.001). There was no statistically significant difference (p=0.496) between YGTSS score improvement and site of DBS electrodes. There was a significant effect favouring DBS over the controlled condition (based on 4 studies). They were unable to quantitatively analyse AEs and side effects.

Cannon *et al*, in a case series of 11 patients showed a mean 49.6% (p<=0.002) reduction in tic severity 3 months post implantation compared with baseline, before surgery (Cannon *et al.*, 2012). An extension of this case series by 16 months and 6 patients (n=17) demonstrated a further reduction in YGTSS scores to a mean of 54.3% (p<=0.001) at final fup compared with baseline (Sachdev *et al.*, 2014). Eight patients required ongoing pharmacotherapy (Sachdev *et al.*, 2014). The mean reduction in Y-BOCS (Yale-Brown obsessive compulsive scale) was 61.9% (p=0.001) and GTSQoL improved by a mean of 68% (p<0.001) between baseline and final fup (Sachdev *et al.*, 2014). In terms of AEs, four patients had cable breakage; one had an infection requiring bilateral lead replacement. Three patients had hardware malfunction that was subsequently corrected. Side effects related to stimulation itself and were mostly temporary and attenuated with adjustment of stimulation parameters. These included: anxiety, agitation, dizziness, poor balance, worsening of pre-existing stuttering and worsening in tic severity (Sachdev *et al.*, 2014).

Another RCT pilot study, by Okun *et al*, randomly allocated five patients to ON, OFF and intermittent scheduled stimulation (Okun *et al.*, 2013). Patients had a mean reduction in total YGTSS score of 19% (p=0.01) and 36% (p=0.01) improvement in MRVRS at 6 months. No significant AEs were reported during this time. An extension to this study by Rossi, completed follow up to 24 months on the same five patients (Rossi *et al.*, 2016). Comparing 24 month fup to baseline, the mean total YGTSS improvement was 30% (range 10%-58%) and the MRVRS showed a mean improvement of 56% (range 21%-81%). On average the total YGTSS score was 14.8% better and the MRVRS was 15.6% better at month 24 compared with month 6.

Does DBS lead to improvement in quality of life in severe medication refractory Tourette patients?

The RCT by Kefalopoulou *et al* (n=13 patients) showed an improvement of 38.9% (95%CI 19.7% - 58%; p=0.001) in GTSQoL scores between baseline and final fup (Kefalopoulou *et al.*, 2015). Two case series studies also reported on quality of life (one was an extension and longer term follow-up of the other) (Cannon *et al.*, 2012, Sachdev *et al.*, 2014). With the proviso that the statistical power of these case series studies is low and that they are descriptive only, so that the findings can only be considered to be hypothesis generating, they did suggest that there was an improvement in QoL. However, this declined from a mean improvement of 102% (p=0.0002) at fup of up to 30 months (Cannon *et al.*, 2012), to a mean improvement of 63% (p<0.001) at longer term fup of a maximum of 46 months (Sachdev *et al.*, 2014).

5. Discussion

Although all studies reported a beneficial effect on tics, as assessed by the YGTSS, the majority were uncontrolled cases with study methods, including levels of stimulation, fup duration and outcomes, varying widely. They were mostly small sample sizes, limiting statistical analysis and generalisability. All of these factors limit meaningful interpretation. The selected studies also targeted different areas of the thalamus, utilising uni and bi-polar electrode activation, making it difficult to ascertain an optimal location for the DBS electrodes and an optimal level of stimulation. Baldermann *et al* suggested that more than one target area in the brain rather than a specific site might be a more effective approach (Baldermann *et al.*, 2016). Additionally, Okun *et al* have demonstrated the potential for scheduled DBS paradigms, as opposed to continuous, and this requires further evaluation (Okun *et al.*, 2013).

Kefalopoulou *et al* had several patients, particularly those showing good response patterns, who required progressive increase in amplitude of stimulation over time, raising the concern that tolerance to stimulation and accelerated battery depletion could occur (Kefalopoulou *et al.*, 2015). Their patients also showed a surprisingly high frequency of infection (13%) suggesting that infection rates might be associated with DBS in patients with TS (Kefalopoulou *et al.*, 2015). They hypothesised that this may be due to tic-related behaviours, co-morbidity or TS-associated immunological profiles, but that this remains unclear (Kefalopoulou *et al.*, 2015).

Adverse events and side effects

None of the identified studies were set up specifically to investigate these outcomes apart from Okun M *et al* that did not show any significant AEs at 6 months fup, but was a pilot study with only five participants (Okun *et al.*, 2013). Other studies reported a number of adverse events including gaze disturbances or transient visual symptoms and lead infections (Ackermans *et al.*, 2011, Cannon *et al.*, 2012). Side effects such as transient mood deterioration and stimulation-dependent dysarthria were most frequently reported (Baldermann *et al.*, 2016). Other side effects included: erectile dysfunction, depressive symptoms, memory impairment, anxiety, weight gain, agitation, constant tiredness and apathy (Baldermann *et al.*, 2016, Ackermans *et al.*, 2011, Cannon *et al.*, 2012, Welter *et al.*, 2008).

Is DBS clinically effective at improving tic severity in severe medication refractory Tourette patients?

All studies showed an improvement in YGTSS scores (see Tables 1 & 2 for details). The definition of the primary outcome varied between studies (one defined it as a reduction of at least 50% and another of at least 40% in order to allow for placebo responses). The exact site of brain stimulation differed between studies, and were either thalamic, globus pallidus (internal or external), or anterior limb of the internal capsule and nucleus accumbens. The level of stimulation also varied together with whether it was uni- or bi-lateral and continuous or scheduled (one study only).

The studies by Kefalopoulou, Ackermans and Baldermann all showed some improvement in MRVRS as well (Kefalopoulou *et al.*, 2015, Ackermans *et al.*, 2011, Baldermann *et al.*, 2016).

Potential limitations and weaknesses of the studies

Small sample size and biased population sample such as the study with men only (Ackermans et al., 2011) reduces the statistical power and external validity of the findings hence limiting generalisability. Influence of co-morbidities on the outcomes was difficult to ascertain and detailed analysis of co-morbidities was limited. Small sample sizes also do not allow analysis of predictors of response. Open label design of studies with a lack of placebo control may have led to both interviewer and patient bias.

Studies rarely reported ongoing pharmacotherapy or changes in pharmacotherapy after DBS as well as co-morbid symptoms. These may well have influenced the outcomes reported in either direction.

These factors were of significant importance to interpretation of the study findings.

Principal indications of the findings

The findings are not robust enough to make any certain recommendation of the use of DBS in severe, medically refractory TS on a routine basis.

Recommendations for further research

- Identification of definitive site/s or region/s of stimulation in the brain
- Identification of factors that predict individual patient responsiveness to DBS
- Long term outcomes
- Influence of co-morbidities on the response to DBS and vice versa.
- Safety – efficacy and side effect profile requires further investigation with appropriately powered and designed studies

6. Conclusion

Based on critical appraisal of the articles identified there is not enough evidence to recommend the routine use of DBS for severe, medically refractory TS at this time.

Table 1: Critical appraisal of the literature identified for DBS to treat refractory Tourette syndrome

Use of DBS to treat refractory Tourette syndrome

| Study reference | Study Design | Population characteristics | Intervention | Outcome measure type | Outcome measures | Results | Quality of Evidence Score | Applicability | Critical Appraisal Summary |
|--|--|--|---|------------------------|--|--|---------------------------|---------------|---|
| Kefalopoulou, Z <i>et al</i> 2015 NCT01647269 | Double blind crossover trial randomised (1:1), in 2 academic centres in the UK (UCL, Institute of Neurology, London & Salford Royal NHSFT, Manchester) 5 Nov 2009 – 16 Oct 2010 continuous stimulation or not in 3 month | 15 adults aged 24yrs – 55 yrs; 11M; 4F; 2 withdrew 1 before and 1 after randomisation (both immediately received open-label continuous stimulation) 4 patients were not on any drugs at enrolment Inclusion criteria: stable Tourette's with YGTSS score of at least 35/55 for at least 12 months before surgery; no response to conventional medical treatment at therapeutic | Bilateral globus pallidus internus (GPi) DBS inserted (13 anteromedial; 2 posteroventral) and randomly assigned to Stimulation off – no stimulation for 3 months followed by stimulation for 3 months Stimulation On – stimulation for the first 3 months followed by no stimulation for the second 3 months; this was followed by an open label phase with permanent on | Primary | YGTSS | Based on 13 patients: mean difference between the on and off stimulation scores (assessed at the end of each 3 month period) was 12.4 (95% CI 0.1 to 24.7; p=0.048), a mean 15.4% improvement; Between baseline and on stimulation showed an improvement of 19.6 points (95% CI 5.0 – 34.3; p=0.009), a mean 22.6% improvement Baseline versus open-label stimulation mean score improvement of 3.1, a mean 22.4% improvement; p=0.09 Baseline and on stimulation (open label phase) percentage improvement 38.9% (95% CI 19.7 – 58.0; p=0.001) 43.2% (95% CI not reported; p=0.025) ON vs OFF stimulation showed a mean improvement score of 1.75 (95% CI 0.16-3.35; p=0.031) | 9 Grade B | Direct | A double-blind, randomised study involving a subset of the population of interest. There was a wide range of improvements during the double blind assessment, with more consistent improvements in tics compared with baseline after the initiation of open label stimulation adjustment. This is common in trials of DBS where adjustment of stimulation while maintaining treatment blinding can compromise the identification of the optimum settings. There is still uncertainty about the best positioning of DBS electrodes in the brain. The study was limited by its small sample size. |
| | | | | Clinical effectiveness | | | | | |
| | | | | Secondary | Yale - Brown obsessive compulsive scale (clinician administered) | | | | |
| | | | | Clinical effectiveness | <i>Gilles de la Tourette syndrome quality of life scale (patient reported)</i> | | | | |
| | | | | Clinical effectiveness | Beck depression inventory (patient) | | | | |
| Clinical effectiveness | <i>MRVRS observed</i> | | | | | | | | |

Table 1: Critical appraisal of the literature identified for DBS to treat refractory Tourette syndrome

Use of DBS to treat refractory Tourette syndrome

| Study reference | Study Design | Population characteristics | Intervention | Outcome measure type | Outcome measures | Results | Quality of Evidence Score | Applicability | Critical Appraisal Summary |
|-----------------|---|--|---|----------------------|------------------|--|---------------------------|---------------|----------------------------|
| | blocks followed by an open label phase; Adjustments or pseudoadjustments of stimulation settings were done in an identical manner Bilateral GPI DBS; bi- or mono-lateral stimulation Continuous Fup: 6-36 months | doses of three classes of drugs; behavioural intervention had been thought inappropriate or had been unsuccessful; optimised treatment of comorbid disorders for at least 6 months; compliant with any psychosocial interventions or surgical treatment plans Exclusion: tic attributable to another disorder; presence of other medical or psychiatric disorders that might increase the risk of the procedure; psychosocial factors that might impede operative or post-operative care and research | stimulation (post hoc analyses based on comparisons with this and baseline); during blinded phase electrical stimulation delivered as single monopolar in 9 patients and double monopolar in the remaining 4 Double blind phase of the study started 7 weeks after surgery Patients followed up monthly, with detailed assessment at the end of each 3 month period | | | | | | |
| | | | | Secondary Safety | | 3 serious AEs: 2 developed infection of DBS hardware necessitating removal and antibiotics (both were subsequently re-implanted successfully); 1 required admission to hospital for alteration of stimulation settings and benzodiazepines | | | |

Table 1: Critical appraisal of the literature identified for DBS to treat refractory Tourette syndrome

Use of DBS to treat refractory Tourette syndrome

| Study reference | Study Design | Population characteristics | Intervention | Outcome measure type | Outcome measures | Results | Quality of Evidence Score | Applicability | Critical Appraisal Summary |
|-----------------|--------------|--|--------------|----------------------|------------------|---------|---------------------------|---------------|----------------------------|
| | | participation; coagulation disorders; other disease compromising life expectancy; likely to benefit from psychological intervention; | | | | | | | |

Draft for consultation

| Study reference | Study design | Population characteristics | Intervention | Outcome | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
|---------------------------------|--|--|--|---|--|---------------------------|---------------|--|
| Ackermans, <i>et al</i> 2011 | Prospective randomized Double blind controlled cross-over clinical trial N=8; 6M, 2F both of whom dropped out after randomisation Patients recruited between February 2005 and April 2008 in one hospital in Maastricht (Netherlands) or one hospital in Ghent (Belgium) Thalamic: CM-Spv-Voi Continuous stimulation in 3 month blocks followed by open label ON | Based on final sample n=6: Patient age range 35 – 48 yrs, mean 40.3 years; mean duration of disease 33 years Inclusion criteria Age >25 years Severely refractory with YGTSS minimum score of 25 Failed to respond or could not tolerate 3 month trial of classical, modern and experimental anti-psychotic medication at adequate | Surgery (electrode implantation at centromedian nucleus – substantia periventricularis-nucleus ventro-oralis internus crosspoint of the thalamus) followed by unblinded adjustment of the stimulation parameters and then either: Group A: ON for 3 months followed by OFF for 3 months Group B: OFF for 3 months followed by ON for 3 months After the blinded cross over period the stimulator was switched ON for 6 months | Primary outcome: change in tic severity measured by: Total YGTSS score in ON vs OFF condition and at 1 year after surgery RVRS at 1 year Secondary outcome – change in associated behavioural disorders and mood assessed before surgery, at | 6/8 patients completed the trial (5 in Group A and 1 in Group B). the analysis is based on these 6 male patients Change in tic severity The YGTSS score was significantly lower during the ON period compared with the OFF period: mean 25.6 (SD 12.8) vs 41.1 (5.4) , p=0.046; a proportionate difference of 37% At one year (open label) follow up there was a significant reduction on both YGTSS (49%) and RVRS (35%) as compared with preoperative assessments (p=0.028 and p=0.046 respectively) Secondary Y-BOCS – No significant difference between ON and OFF states (mean difference 1.3 (p=0.686) or between 1 year fup and before surgery (mean difference 5.8; p=0.249) Behavioural disorders and mood: Neuropsychological test scores before and 1 year after surgery revealed no significant changes except for time taken to complete the colour word card of the Stroop test (measures | 7 Grade B | Direct | Unblinded adjustment parameters immediately after surgery took 3 weeks for 5 patients and 5 months for one because of a complex psychiatric situation. All patients were male; 2 female patients dropped out after randomisation; dilution of crossover effect as only 1 patient was in Group B; unblinded adjustment of parameters may have allowed patients to know whether they were in the ON or OFF stimulation phase of the trial Only 2/6 patients completed the full 3 months OFF and 3 months ON periods Small sample size and high risk of Type 2 errors may have resulted in underestimation of negative cognitive effects Impact of co-morbid effects on outcomes difficult to ascertain e.g. one patient had a history of alcohol abuse |

| | | | | | | | | |
|------------------------------|--|---|---|--|---|--|--|--|
| | <p>for 6 months</p> <p>Bilateral quadripolar electrodes; DBS always performed bilaterally; mono- or bipolar stimulation</p> <p>Follow up 12 months</p> | <p>doses</p> <p>All had completed at least 10 sessions of behavioural therapy including habit reversal or exposure in vivo</p> | | <p>the end of each blinded condition and at 1 year follow up.</p> | <p>selective attention and response inhibition), which increased.</p> <p>Adverse events</p> <p>3 patients had AEs related to surgery: 1 small parenchymal haemorrhage resulting in vertical gaze palsy that resolved after 6 months</p> | | | |
| <p>Ackermans L 2011 ctd.</p> | | <p>Exclusion criteria</p> <p>Tics not related to Tourette syndrome</p> <p>Severe cognitive impairment</p> <p>Major psychiatric disorder</p> <p>Current substance abuse or dependence (excluding tobacco)</p> <p>Structural</p> | <p>Evaluations by a clinician were performed at : the end of each condition (ON or OFF), at 3&6 months after surgery and at 1 year post surgery</p> | <p>Tests used:</p> <p>Conners ADHD rating scale; Y-BOCS; Beck Anxiety Inventory, Visual Analogue Scale for self-injurious behaviour</p> <p>Cognition:</p> <p>Neuropsychological tests (before surgery and at 1 year</p> | <p>1 patient developed a staphylococcus aureus infection in the infraclavicular region, which was successfully treated with 6 weeks of IV antibiotics</p> <p>1 patient had varying motor and psychiatric symptoms up to 1 year post operatively e.g. lethargy, binge eating, frequent falls. These symptoms were not affected by adjusting parameter settings or switching to OFF. A CT scan at 6 months showed cerebral atrophy that had not been there previously</p> <p>1 patient developed severe multidirectional nystagmus when stimulation was OFF (occurred after the 1 year period of evaluation and 3 years after the surgery)</p> <p>All patients reported a lack of energy substantially restricting their daily activities & visual disturbances varying from blurred vision to fixation</p> | | <p>The difference between open label and unblinded scores for YGTSS (49% vs 37%) may have been due to placebo effects. Patients with TS are known to be suggestible.</p> <p>There was no stimulation effect on associated behavioural disorders and mood for the total group. This could have been due to symptoms being subclinical or mild in all patients prior to surgery</p> <p>Stroop changes suggest a decrease in selective attention and response inhibition</p> <p>Small sample size and resulting reduced statistical power and external validity limit the</p> | |

| | | abnormalities on brain MRI CI to surgery or anaesthesia | | follow up) | problems although no objective abnormalities were detected by an optometrist and neuro-ophthalmologist | | | generalisability of this study Further RCTs are required to identify the optimal target in the brain to stimulate |
|------------------------------------|--|--|--|---|--|---------------------------|---------------|--|
| Study reference | Study design | Population characteristics | Intervention | Outcome | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
| Welter M-L 2008 NCT00139308 | Controlled double blind RCT cross-over design PILOT Paris, France Bilateral quadripolar electrodes in CM-Pf (limbic) and GPi (ventromedial part) Continuous Fup: 20-60 months | 3 patients 2F (36,30 yrs); 1M (30yrs) Inclusion criteria: TS as classified by DSM IV >18 years of age Severe disease adversely affecting social integration Failure of best treatment by medication or intolerance after a | Implantation of 4 quadripolar electrodes within the left and right CM-Pf and 2 within the left and right GPi connected to 2 subclavicular implanted programmable pulse generators Patients examined 1 month before surgery, 2 months after surgery without stimulation, after which 4 stimulation conditions were individually randomly assigned in a crossover design (n of 1 design study): | Primary Tic severity: YGTSS Motor and phonic tic subscore (YGTSS less 50 point impairment portion) Other Rush Video-Based Tic Rating Scale (RVRS) Psychiatric symptoms: depression, anxiety, impulsiveness, obsessive- | 3 patients Compared with pre-operative assessment the best improvement in tic severity was with GPi stimulation with a reduction in YGTSS of 65%, 96% and 74% in patients 1, 2 and 3 together with an 80%, 90% and 67% reduction in motor and phonic tic subscore For CM-Pf these figures were: YGTSS 64%, 30%, 40% and 41%, 37%, 41%. Combined pallidal and thalamic stimulation did not improve tic reduction further (YGTSS 60%, 43%, 76%; motor and phonic subscore 59%, 16%, 70%) RVRS – presented graphically only Adverse effects Thalamic stimulation: transient cheiro-oral or arm paresthesias (a few minutes); decreased libido in 1 patient | 6 Grade C | Direct | Small sample size limits generalisability No statistical analysis done (small sample size) More of a hypothesis generation study |

| | | <p>minimum of 6 months of treatment</p> <p>Absence of cognitive deficits or psychosis</p> <p>Ability to provide written informed consent</p> | | <p>compulsive behaviours</p> <p>Neuropsychological status: attention, episodic memory, working memory, flexibility</p> | <p>Pallidal: lethargy (3-4 days); nausea and vertigo with increasing intensity of stimulation in 2/3 patients, anxiety in 1 patient</p> | | | |
|-----------------|--------------|--|---|--|---|---------------------------|---------------|----------------------------|
| Study reference | Study design | Population characteristics | Interventions | Outcomes | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
| | | | <ol style="list-style-type: none"> 1. Bilateral thalamic 2. Bilateral pallidal 3. Bilateral thalamic & pallidal 4. No stimulation (sham) <p>Assessments every month during a 5-day hospitalisation</p> <p>An open label long-term follow up evaluation was done at 60 months for patient 1, 33 months for patient 2 and 20 months for patient 3</p> | | | | | |

| Study reference | Study design | Population characteristics | Intervention | Outcome | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
|------------------------|---|---|--|---|--|--|---------------|---|
| Baldermann J-C 2016 | Systematic review and meta-analysis Inclusion: English or German; clinical trials or case reports of GTS; original published and peer reviewed articles 4 studies included in calculation of effect size and the forest plot Whether DBS electrodes were bilateral, uni-or mono-polar activation or continuous stimulation was not reported for the individual studies | Qualitative synthesis: 57 articles reporting a total of 162 patients (individual studies had between 1 and 17 patients) Quantitative Meta-analysis: 48 studies; 150 patients, six of whom had two different target points resulting in 156 cases analysed Median age at operation 30.0 +/- 9.8 years (range 15-60) Median symptom onset age 7.0 +/- 3.3 (range 1-23) | DBS for Tourette Site/brain targets of electrodes in cases: 78 thalamus; 44 in Gpi-am; 20 in GPI-pl; 9 in ALIC-Nac;; 1 GPe; 4 Other Outcome measures for time categories (<= 3, 6, or 12 months or >12 months) compared with baseline T0 | YGTSS total score (global YGTSS) baseline compared to last reported clinical follow up Additional subgroup analysis for different brain targets Secondary Sub-scores of YGTSS (motor & vocal tics) MRVRS BDI Y-BOCS | Primary Significant decrease in median score: 83.0 to 35.0 at last available follow up, resulting in a median improvement of 52.68% (n=156; IQR=40.83; p<0.001) Median improvement rates of 48% for tic severity (n=73; IQR=47.84; p<0.001) Analysis of the different time categories showed that the main decrease occurred in the first postoperative months and dropped further afterwards Subgroup analysis different brain targets: Thalamic: median decrease 47.62% (IQR=43.61; p<0.01) GPI-pl: median decrease 58.03% (IQR=61.09; p<0.001) GPI-am: median decrease 55.32% (IQR=38.13;p<0.001) ALIC-Nac: median decrease 44.00% (IQR=24.58; p=0.018) No significant difference (p=0.496) between all of the targets (thalamus, GPI-am, GPI-pl, ALIC-Nac) Overall statistically significant effect | 9 (for SR & MA) Grade C (for studies included in SR & MA) | Direct | One researcher extracted the data and a second researcher independently checked the data extraction forms for accuracy and completeness. Duplicates were excluded. Mainly based on studies of evidence level IV (American Academy of Neurology classification). Global YGTSS compared at T0 and last available follow up, which may lead to an over- or under-estimation of effect. Applied stimulation settings were often not reported so their influence on the results was not able to be assessed. Likewise, ongoing pharmacotherapy or changes in pharmacotherapy after DBS as well as comorbid symptoms were also rarely reported. No conclusive answer as to which area is the ideal target to stimulate. It may be ideal to stimulate more than one target in any case. Analysis of pooled data from patients who underwent stimulation in different regions of |

| | | 97.8% pre-operative YGTSS value >50 | | | <p>size (4 studies): 0.96 (CI: 0.42-1.58), heterogeneity $I^2=0\%$, favouring DBS over the controlled condition</p> <p>Secondary</p> <p>Motor tics: median decrease 38.56% (n=71; IQR=26.31; p<0.001)</p> <p>Vocal tics: median reduction 40.0% (n=70; IQR=35.26; p<0.001)</p> <p>MRVRS: median improvement of 48% (n=27; IQR=11.73; p<0.001)</p> <p>Y-BOCS – median reduction of 31.25% (n=112; IQR=46.24); median preoperative score=16.0, IQR=10.6; median postoperative score 10.7, IQR=12.0. Subgroup analysis did not show significant differences between targets (p=0.812)</p> <p>Adverse events & side effects</p> <p>Quantitative analysis of these was not possible</p> | | | <p>the brain can only give a rough overview and ignores the complex neuroanatomy of the brain.</p> <p>Conclusion: despite the limitations above, DBS is a valid option for GTS in otherwise therapy-resistant patients. However, efficacy and side effect profile requires further investigation with appropriately powered and designed studies.</p> |
|-----------------|---|---|--|--|--|---------------------------|---------------|---|
| Study reference | Study design | Population characteristics | Intervention | Outcome | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
| Cannon E 2012 | Case series (time period Sept 2008- Dec 2010) bilateral amGPi | Australia (Brisbane, Queensland); 1 hospital 11 patients with severe, medically | Surgical implantation of Medtronic quadripolar electrodes bilaterally in GPi Follow-up: weekly for 1 month, monthly for | Primary YGTSS 50% mean reduction | Primary Overall there was a reduction in the mean total score from 84.45% before surgery to 42.55% 3 months after surgery ; a 49.6% reduction in total tic severity (p<=0.002) | 6 Grade C | | <p>The results suggest that the GPi is a safe and effective target for severe and treatment refractory TS as well as its common co-morbid symptoms such as OCD and depression.</p> <p>Open label design, without</p> |

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| | <p>Continuous Fup 4-30 months</p> | <p>intractable TS (all had tried between 3 and 6 different medications)</p> <p>8/11 (73%) men</p> <p>Age: mean 39 yrs; range 18-50 years</p> <p>Duration of TS range: 14-45 yrs</p> <p>Inclusion: DSM IV TR diagnosis; severe TS; documented non-response to multiple pharmacotherapies; medical suitability for surgery; ability to provide informed consent</p> <p>Exclusion: <18 yrs; other cause of tics</p> | <p>3 months then quarterly</p> <p>Stimulation parameters adjusted as necessary</p> <p>Rating scale assessments at T0 (before surgery), 1 month after surgery and at final follow up (mean 14 months, range 4-30 months)</p> | <p>Secondary</p> <p>Y-BOCS</p> <p>Hamilton Depression rating scale</p> <p>GTS QoL scale</p> <p>Global assessment of functioning scale</p> | <p>1 patient switched off the stimulator after 3 months owing to numerous somatic complaints e.g. fuzzy head, feeling overheated</p> <p>Secondary</p> <p>Y-BOCS- overall reduction in mean score from 15.82 to 6.55 (59%)</p> <p>HAM-D – reduction in mean score 16.45 to 4.27 (74%) at month 1 and further improved at month 3</p> <p>GTS-QoL-at final follow up compared to baseline, improvement from 39.09 to 79.09 (p=0.001): 102% mean improvement</p> <p>Global assessment of functioning scale: improving from 47.27 at baseline to 74.55 at final follow up (p=0.0002):58% mean improvement</p> <p>Overall there was a significant reduction in the requirement for pharmacotherapy following DBS</p> <p>Adverse events & side effects</p> <p>Increased tic severity reported in 1 patient</p> <p>3 patients: hardware malfunction: lead damage or breakage caused by car crash, tic severity and one cause unknown</p> <p>2 patients increase in anxiety, one with</p> | | <p>placebo control, prone to interviewer and patient bias. However, sustained response and recurrence of symptoms when DBS inadvertently interrupted in a few cases argues against a placebo effect</p> <p>Small sample size – does not allow predictors of a good response or detailed analysis of comorbidities.</p> <p>Study design and small sample size limit generalisability</p> |
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| Study reference | Study design | Population characteristics | Interventions | Outcome | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
|------------------|--|---|---|---|--|---------------------------|---------------|--|
| | | | | | <p>panic attacks</p> <p>1 patient lead infection requiring bilateral lead replacement</p> <p>There were no intraoperative or immediate postoperative complications</p> | | | |
| Sachdev, PS 2014 | <p>Extension of case series (Cannon E <i>et al</i>, see above)</p> <p>Australia; 2 hospitals: 1 New South Wales; 1 Queensland</p> <p>Additional 6 patients</p> <p>Fup extended to a maximum of 46 months</p> | <p>An additional 6 patients (patients 12-17) and longer term fup of all patients to a maximum of 46 months</p> <p>N=17</p> <p>14M, 3F</p> <p>Mean age 29.1 years (range 17-51)</p> <p>2 patients <18 years had consent for surgery obtained in the presence of their mothers</p> | <p>Final assessment at a mean 24.1 months (range 8-46 months) following surgery</p> <p>Response defined as >50% reduction in total YGTSS score</p> | <p>Primary</p> <p>YGTSS</p> <p>Secondary</p> <p>Y-BOCS</p> <p>Hamilton Depression rating scale</p> <p>GTS-QoL scale</p> <p>Global assessment of functioning scale</p> | <p>Primary</p> <p>12/17 (70.6%) responded to DBS, with a >50% reduction in YGTSS score</p> <p>Overall there was a reduction in mean total YGTSS score of 54.3% (p<=0.001) between T0 and final assessment</p> <p>48.3% reduction in motor and 41.3% reduction in phonic tics at 1 month, and this improvement was maintained at final fup</p> <p>8 patients required ongoing pharmacotherapy</p> <p>Secondary (T0 vs final assessment)</p> <p>Y-BOCS – mean score decreased from 13.88 at T0 to 5.29 (mean reduction at the final assessment (p=0.001)</p> <p>HDRS – mean score reduced from 15.35 to 8.00 (p=0.001)</p> <p>GTS-QoL – improved from 40.88 to</p> | | | <p>As for Cannon E <i>et al</i> (2012)</p> <p>On the whole, the findings suggest that time to respond to antero-medial Gpl DBS is short, being between 1-3 months and the symptomatic gains, once achieved, remain stable over time.</p> <p>The lack of comparison site of stimulation makes it difficult to assess whether this is an optimal implantation site.</p> <p>Longer term fup data of effect of stimulation and worsening of tics when switched off further support the argument against this being a placebo response to DBS</p> |

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| | | | | <p>66.47 ($p < 0.001$); a mean improvement of 63%</p> <p>GAF – improved from 50.0 to 72.12 ($p < 0.001$); a mean improvement of 44%</p> <p>Outliers</p> <p>Patient 9 responded at the first wave of fup, but had battery failure leading to severe tic recurrence and relapse of pre-DBS pattern of substance abuse eventually leading to removal of the device</p> <p>Patient 11 had worsening of tics and somatic symptoms with the stimulation and chose to have the device switched off at month 3.</p> <p>Adverse effects</p> <p>4 patients had cable breakage (the fourth by self-injurious tic); 1 patient had infection around the leads in the neck 3 months after surgery requiring bilateral lead replacement; 3 patients had hardware malfunction with interrupted stimulation and associated worsening of tics that improved once stimulation was re-established.</p> <p>Side effects</p> <p>Related to stimulation itself and were mostly temporary and attenuated with adjustment of stimulation parameters. These included: anxiety, agitation, dizziness, poor balance, worsening of pre-existing stuttering and worsening</p> | | |
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| Study reference | Study design | Population characteristics | Intervention | Outcome | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
|-----------------|---|---|---|--|--|---------------------------|---------------|--|
| Okun MS 2013 | <p>Clinical trials planning study</p> <p>1 university movement disorders centre; Florida, USA</p> <p>RCT – randomised to treatment timing; blinding of patients and treatment physicians</p> <p>Thalamic: CM</p> <p>Scheduled stimulation</p> <p>Fup 6 months</p> <p>Inclusion criteria: DSM-IV diagnosis of TS; YGTSS total score >35 with motor score >15</p> <p>TS-caused incapacitation</p> | <p>N=5</p> <p>M2; F3</p> <p>Mean age 34.4 years (range 28-39), mean disease duration 28.8 years (range 20-37 years)</p> <p>Pre-surgical mean YGTSS total score was 92.2+/-9.34 and MRVRS total score was 16.6 +/-1.95</p> | <p>To assess whether scheduled intermittent DBS was as efficacious as continuous DBS</p> <p>Insertion of bilateral cranially placed neurotransmitters (NeuroPace) in the centromedian thalamic region</p> <p>3 settings for each patient (randomly assigned): continuous; off; intermittent scheduled</p> <p>Settings were tailored to each patient and varied from 1.0 to 4.5 mA and could also vary from one side of the brain to the other. If the stimulation was “too much” for a patient, they could use a cranial handheld magnet swipe to turn off the DBS for 1 hour</p> | <p>50% improvement in YGTSS total (motor and phonic) score</p> <p>Secondary</p> <p>Includes Y-BOCS, MRVRS, Hamilton Depression rating scale</p> | <p>in tic severity (patient 11)</p> <p>YGTS total score reduced by 5%, 16%, 16%, 26% and 30% for the 5 patients. None of the subjects achieved the pre-study success criterion of 50%.</p> <p>The mean reduction was 17.8 (SD 9.4), p=0.01</p> <p>36% mean improvement in mean total MRVRS score</p> <p>No significant adverse effects at 6 months</p> | 6 Grade C | Direct | <p>Planning study with small number of patients.</p> <p>Raises some interesting points for future study:</p> <p>Cranial contained implant may lessen risk of infection and curb lead and connector fractures e.g. due to neck and shoulder tics</p> <p>Scheduled stimulation may prolong battery life and possibly less stimulation induced tolerance.</p> <p>Provides proof of concept that scheduled DBS could visibly suppress motor and vocal tics in a group of individuals with medication-refractory TS</p> |

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| <p>with severe distress, self-injurious behaviour and/or qol disruption; >25 years; medication refractory (tics present despite appropriate doses of at least 3 dopamine-blockers and a single alpha 2 adrenergic agonist; had to have been offered behavioural therapy</p> <p>Exclusion:</p> <p>Psychosis; anxiety; depression; bipolar disorder or any other Axis I psychiatric disorder; severe medical co-morbidities that would potentially affect suitability for surgery; other non-TS</p> | | | | | | | | |
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Draft for consultation

| Study reference | Study design | Population characteristics | Intervention | Outcome | Results | Quality of Evidence score | Applicability | Critical appraisal summary |
|-------------------|---|------------------------------|---|--|---|---------------------------|---------------|---|
| Rossi; PJ 2016 | <p>Extended (to 24 month) follow up of patients described in Okun MS 2013 pilot study.</p> <p>Also presents a responder analysis (defined as >40% improvement in YGTSS total score and/or MRTRS total score). This was lower than the 50% chosen in the planning trial and selected to be the threshold for minimum</p> | See Okun MS 2013 pilot study | <p>Pulse train (duration and spacing of stimulation delivery): given as a ratio of ON:OFF</p> <p>Duty cycle (defined by one or more blocks of time of variable duration in which pulse trains were delivered): range 0.5-24h and occurred between 1 and 4 times per day</p> <p>Total cycling time (total number of scheduled hours within a 24h period that fixed pulse trains of stimulation were delivered): 2-24h</p> <p>Total daily stimulation</p> | <p>YGTS total score</p> <p>MRTRS total score</p> | <p>Baseline versus 24 month</p> <p>YGTS: improvement by 10%, 46%, 58%, 17% for the 4 active study subjects (1 lost to fup). Mean improvement across the cohort 30% (range 10-58%).</p> <p>Subject lost to fup had 18% improvement at month 18 (final measure)</p> <p>Full responder status achieved by 2/4 patients (50%)</p> <p>MRTRS: improved by 21%, 79%, 81%, 44%. Mean improvement across the cohort 56% (range 21-81%). Subject lost to fup showed a 19% improvement at month 18.</p> <p>Full responder status achieved by ¾ patients (75%)</p> <p>The subject lost to fup was classified as</p> | 6 Grade C | Direct | <p>Small sample size limiting power and generalisability</p> <p>Improvements in total YGTSS And MRTRS scores were not uniform across the 6 month fup periods. This may have been due to changes in stimulation parameters.</p> <p>It is worth considering that scheduled stimulation may function differently to continuous stimulation and that responses may not match those previously seen in continuously stimulated subjects.</p> <p>Electrical stimulation of the centromedian thalamic region in a scheduled paradigm was effective in suppressing tics, particularly phonic tics. Full responders were</p> |

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| | meaningful clinical improvement above the estimated placebo effect. | | time (amount of time within a 24h period that electrical current was actually emitted from the implanted electrode): 0.5-5h DBS programming sessions were performed at each 6-month follow up interval | | a non-responder (<25% improvement) for both YGTSS and MRTRS at month 18. Responders: mean stimulation time 1.85h per day On average, YGTSS total score was 14.8% better at month 24 vs month 6; MRVRS total score was 15.6% better at month 24 vs month 6 | | | able to achieve the positive DBS effect with a mean of 2.3 +/-0.9 (SEM) hours of DBS per day |
|--|---|--|---|--|---|--|--|--|

YGTS – Yale global tic severity scale; Y-BOCS – Yale-Brown obsessive compulsive scale; GTS-QoL – Gilles de la Tourette syndrome quality of life scale; MRVRS – modified Rush video-based tic rating scale; RVRS-Rush video-based tic rating scale (not modified)

GTS – Gilles de la Tourette syndrome

CM-Pf – centromedian-parafascicular complex of the thalamus; CM-Spv-Voi - centromedian nucleus – substantia periventricularis-nucleus ventro-oralis internus crosspoint of the thalamus; GPe - external globus pallidus; GPi – internal globus pallidus; ALIC-Nac – anterior limb of the internal capsule and nucleus accumbens

Fup-follow-up; mo-months; yrs-years

Table 2: Summary of outcome measures by study (Grade B studies only)

| Outcome Measure | Reference | Quality of Evidence Score | Applicability | Grade of Evidence | Interpretation of Evidence |
|---|---------------------|---------------------------|---------------|---|--|
| Yale Global Tic Severity Scale (YGTSS) | Kefalopoulou Z 2015 | 8 | Direct | B | Double blind RCT comparing OFF with ON stimulation for three months each followed by an open label ON stimulation phase, analysis based on 13/15 patients aged between 24-55 yrs. The mean difference between the ON and OFF stimulation scores was 12.4 (95%CI 0.1-24.7; p=0.048), a mean 15.4% improvement. Comparing baseline and ON stimulation showed an improvement of 19.6 points (95% CI 5.0-34.3; p=0.009), a mean improvement of 22.6%. |
| | Ackermans, L 2011 | 7 | Direct | B | Prospective double blind cross-over RCT comparing ON versus OFF stimulation for 3 months each followed by ON stimulation for 6 months (end point 1 year after start of trial). Analysis was based on 6/8 patients aged between 21 and 48 years at DBS, all of whom were male. The YGTSS score was significantly lower during the ON period compared with the OFF period: mean 25.6 (SD 12.8) vs 41.1 (SD 5.4), p=0.046; a proportionate difference of 37%. At 1 year fup, there was a significant 49% (p=0.028) reduction in YGTSS compared with baseline. |
| | Baldermann J-C 2016 | 9 (for SR) | Direct | C for studies included in SR; B for SR itself | Systematic review and meta-analysis incorporating 57 studies reporting a total of 162 patients (qualitative synthesis) and 48 studies involving 156 cases analysed (quantitative synthesis). There was a significant decrease in median score: declining from 83.0 to 35.0 at the last available fup, resulting in a median improvement of 52.68% (n=156; IQR=40.83; p<0.001). There was a median improvement rate of 48% for tic severity (n=73; IQR=47.84; p<0.001). |
| Modified Rush Video-based tic rating scale (MRVRS) | Kefalopoulou Z 2015 | 8 | Direct study | B | Double blind RCT comparing OFF with ON stimulation for three months each followed by an open label ON stimulation phase, analysis based on 13/15 patients aged between 24-55 yrs. ON vs OFF stimulation showed a mean improvement score of 1.75 (95% CI 0.16-3.35; p=0.031) |
| | Ackermans, L 2011 | 7 | Direct | B | Prospective double blind cross-over RCT comparing ON versus OFF stimulation for 3 months each followed by ON stimulation for 6 months (end point 1 year after start of trial). Analysis was based on 6/8 patients aged between 21 and 48 years at DBS, all of whom were male. At one year (open label) fup there was a significant improvement in MRVRS score of 35% (p=0.046) |

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|---|------------------------|------------|--------|---|--|
| | Baldermann J-C 2016 | 9 (for SR) | Direct | C for studies included in SR; B for SR itself | Systematic review and meta-analysis incorporating 57 studies reporting a total of 162 patients (qualitative synthesis) and 48 studies involving 156 cases analysed (quantitative synthesis). There was a median improvement of 48% (n=27; IQR=11.73; p<0.001) in the MRVRS score. |
| Gilles de la Tourette syndrome quality of life scale (GTS-QOL) | Kefalopoulou Z 2015 | 8 | Direct | B | In this double blind RCT comparing OFF with ON stimulation for three months each followed by an open label ON stimulation phase, analysis based on 13/15 patients aged between 24-55 yrs. Comparing baseline and ON stimulation (open label phase) showed an improvement of 38.9% (95% CI 19.7-58.0; p=0.001) in the TSQOL score. |
| Yale Brown Obsessive Compulsive scale (Y-BOCS) | Kefalopoulou Z 2015 | 8 | Direct | B | In this double blind RCT comparing OFF with ON stimulation for three months each followed by an open label ON stimulation phase, analysis based on 13/15 patients aged between 24-55 yrs. They found a baseline versus open-label stimulation mean score improvement of 3.1, a mean 22.4% improvement; p=0.09 |
| | Ackermans, L 2011 | 7 | Direct | B | Prospective double blind cross-over RCT comparing ON versus OFF stimulation for 3 months each followed by ON stimulation for 6 months (end point 1 year after start of trial). Analysis was based on 6/8 patients aged between 21 and 48 years at DBS, all of whom were male. There was no significant difference between ON and OFF states (mean difference 1.3 (p=0.686) or between 1 year fup and before surgery (mean difference 5.8; p=0.249) |
| | Baldermann J-C 2016 | 9 (for SR) | Direct | C for studies included in SR; B for SR itself | Systematic review and meta-analysis incorporating 57 studies reporting a total of 162 patients (qualitative synthesis) and 48 studies involving 156 cases analysed (quantitative synthesis). Y-BOCS – median improvement of 31.25% (n=112; IQR=46.24); median preoperative score=16.0, IQR=10.6; median postoperative score 10.7, IQR=12.0. Subgroup analysis did not show significant differences in response between brain targets (p=0.812) |
| Adverse events (AEs) | Kefalopoulou Z 2015 | 8 | Direct | B | In this double blind RCT comparing OFF with ON stimulation for three months each followed by an open label ON stimulation phase, analysis based on 13/15 patients aged between 24-55 yrs. Three serious AEs occurred: two developed infection of DBS hardware necessitating removal and antibiotics (both were subsequently re-implanted successfully); one required admission to hospital for alteration of stimulation settings and benzodiazepines |
| | Ackermans, L 2011 | 7 | Direct | B | Prospective double blind cross-over RCT comparing ON versus OFF stimulation for 3 months each followed by ON stimulation for 6 months (end point 1 year after start of trial). Analysis was based on 6/8 patients aged between 21 and 48 years at DBS, all of whom were male. 3 patients had AEs related to surgery: the most severe was a small parenchymal haemorrhage in one patient resulting in vertical gaze palsy that resolved after 6 months; 1 patient developed a staphylococcus aureus infection in the infraclavicular region, which was successfully treated with 6 weeks of IV antibiotics; 1 patient had varying motor and psychiatric symptoms up to 1 year post operatively e.g. lethargy, binge eating, frequent falls. These symptoms were not affected by adjusting parameter settings or switching to OFF. A CT scan at 6 months showed cerebral atrophy that had not been there previously |

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| | | | | | <p>After the 1 year period of evaluation and 3 years after the surgery, 1 patient developed severe multidirectional nystagmus when stimulation was OFF</p> <p>One year after surgery, all patients reported a lack of energy substantially restricting their daily activities & visual disturbances varying from blurred vision to fixation problems although no objective abnormalities were detected by an optometrist and neuro-ophthalmologist</p> |
|--|--|--|--|--|--|

YGSS This comprises an assessment of motor and phonic tics In terms of their number, frequency, complexity, intensity and interference with behaviour (Max score= 50). A separate section quantifies the impairment caused by the tics (Max score =50). An impact on this scale demonstrates proof of concept that electrical stimulation can reduce the severity of tics.

Draft for consultation

Appendix 1

Literature search strategy

Terms used:

| Patient/Population/Problem | Intervention | Comparison | Outcome |
|----------------------------|------------------------|------------|---------|
| Tourette Syndrome | Deep Brain Stimulation | | |

The complete search strategy is in the [Appendix](#).

Limits applied:

| Age group | Language | Publication type | Time limit |
|--------------|----------|------------------|------------|
| Not children | English | Any | 2006-2016 |

Disclaimer

Although every effort has been made to ensure this information is accurate, it is possible it may not be representative of the whole body of evidence available. Both articles and internet resources may contain errors or out of date information. None of the resources have been critically appraised. No responsibility can be accepted for any action taken on the basis of this information.

Summary of resources searched and results:

| Source | Results |
|------------------|---|
| EMBASE | 283 |
| MEDLINE | 174 |
| PSYCINFO | 127 |
| COCHRANE LIBRARY | 16 |
| NHS EVIDENCE | 1 |
| TRIP DATABASE | 16 |
| TOTALS | 617 before removing duplicates 383 after deduplication 343 after removing non-relevant items (these stored in Trash folder) |

Search strategies

Embase (Ovid)

| | | |
|----|--|---------|
| 1 | *Gilles de la Tourette syndrome/ | 3008 |
| 2 | "Tourette*" .ab,kw,ti. | 4229 |
| 3 | 1 or 2 | 4358 |
| 4 | brain depth stimulation/ | 29096 |
| 5 | deep brain stimulation.ab,kw,ti. | 12700 |
| 6 | thalamic stimulation.ab,kw,ti. | 431 |
| 7 | 4 or 5 or 6 | 29718 |
| 8 | 3 and 7 | 555 |
| 9 | controlled clinical trial/ or clinical trial/ or controlled study/ or randomized controlled trial/ | 5090264 |
| 10 | case control study/ or case report/ or case study/ | 1488645 |
| 11 | observational study/ | 118499 |
| 12 | "review"/ | 1669170 |
| 13 | "systematic review"/ | 139007 |
| 14 | meta analysis/ | 143531 |
| 15 | (review or meta analysis or random* or RCT case* or trial* or study or control*).m_titl. | 1673428 |
| 16 | 9 or 10 or 11 or 12 or 13 or 14 or 15 | 8748124 |
| 17 | 8 and 16 | 319 |
| 18 | limit 17 to (english language and yr="2006 -Current") | 283 |

Medline (Ovid)

| | | |
|----|--|---------|
| 1 | *Tourette Syndrome/ | 3392 |
| 2 | "Tourette*".ab,kf,kw,ti. | 4553 |
| 3 | 1 or 2 | 4756 |
| 4 | Deep Brain Stimulation/ | 6241 |
| 5 | deep brain stimulation.ab,kf,kw,ti. | 7825 |
| 6 | thalamic stimulation.ab,kf,kw,ti. | 500 |
| 7 | 4 or 5 or 6 | 9676 |
| 8 | 3 and 7 | 292 |
| 9 | randomized controlled trial/ | 432375 |
| 10 | exp clinical trial/ | 759901 |
| 11 | clinical study/ | 2523 |
| 12 | controlled clinical trial/ | 91772 |
| 13 | Case-Control Studies/ | 226403 |
| 14 | case reports/ | 1829070 |
| 15 | review/ | 2198483 |
| 16 | meta-analysis/ | 74054 |
| 17 | observational study/ | 26733 |
| 18 | (review or meta analysis or random* or RCT case* or trial* or study or control*).ti. | 2008043 |
| 19 | 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 | 6305895 |
| 20 | 8 and 19 | 203 |
| 21 | limit 20 to (english language and yr="2006 - 2016") | 174 |

1. PsycInfo; TOURETTE SYNDROME/; 2833 results.
2. PsycInfo; tourette*.ti,ab; 3494 results.
3. PsycInfo; 1 OR 2; 3605 results.
4. PsycInfo; DEEP BRAIN STIMULATION/; 2526 results.
5. PsycInfo; "deep brain stimulation".ti,ab; 2990 results.
6. PsycInfo; "thalamic stimulation".ti,ab; 153 results.
7. PsycInfo; 4 OR 5 OR 6; 3330 results.
8. PsycInfo; 3 AND 7; 131 results.
9. PsycInfo; 8 [Limit to: Publication Year 2006-2016]; 127 results.

Cochrane Library

| | | |
|----|--|---|
| #1 | "deep brain stimulation":ti,ab,kw (Word variations have been searched) | 522 |
| #2 | MeSH descriptor: [Deep Brain Stimulation] explode all trees | 243 |
| #3 | #1 or #2 | 522 |
| #4 | tourette*:ti,ab,kw | 273 |
| #5 | MeSH descriptor: [Tourette Syndrome] explode all trees | 164 |
| #6 | #4 or #5 | 273 |
| #7 | #3 and #6 | 17 (16 records from CENTRAL downloaded, 0 reviews, 1 HTA not downloaded, foreign language document) |

NICE Evidence:

"deep brain stimulation" and tourette*

1 results downloaded.

Trip Pro:

(title:tourette syndrome)(title:deep brain stimulation) 16 results

Trip Trip is a clinical search engine designed to allow users to quickly and easily find and use high-quality research evidence to support their practice and/or care.

Appendix 2

Population, Intervention, Comparator and Outcomes (PICO) template

Literature Search Terms

| Search Terms <i>Indicate all terms to be used in the search</i> | |
|---|--|
| <p>P – Patients / Population</p> <p>Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?</p> | <p><i>Search terms.</i></p> <p><i>Tourette syndrome; Tourette’s syndrome; Gilles de la Tourette syndrome; Refractory Tourette syndrome</i></p> <p><i>The subpopulation of patients to be considered for DBS comprises only those individuals who have failed adequate attempts at treatment with at least 3 medication subclasses, (antipsychotics, atypical antipsychotics, alpha agonists and benzodiazepines), and are either inappropriate for or non responsive to behavioural therapies.</i></p> <p><i>The Population to be considered is adults aged 18 years and above at the time of surgery. There are insufficient data on the long term outcomes of DBS in patients with Tourette syndrome below 18 years old.</i></p> |
| <p>I – Intervention</p> <p>Which intervention, treatment or approach should be used?</p> | <p><i>Search terms.</i></p> <p>Stimulation; Deep Brain Stimulation; DBS</p> <p>Deep brain stimulation involves invasive neurosurgery targeting the network of basal ganglia regions known to be involved in the generation of motor and phonic tics characteristic of Tourette syndrome. Implantation of a subcutaneous pacemaker allows the delivery of tiny amounts of electrical stimulation to precise brain regions as a long term therapy.</p> |
| <p>C – Comparison</p> <p>What is/are the main alternative/s to compare with the intervention being considered?</p> | <p>The effectiveness of Deep Brain stimulation can be objectively evaluated by comparing baseline pre-operative tic severity with post-operative tic severity after optimal stimulation parameters have been derived. Alternatively effectiveness can be judged by comparing tic severity between the ON stimulation and OFF stimulation conditions.</p> |
| <p>O – Outcomes</p> <p>What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity</p> | <p><i>Critical to decision-making:</i></p> <p>The most commonly used outcome measure is the Yale Global Tic severity scale (YGTSS). This comprises an assessment of motor and phonic tics In terms of their number, frequency, complexity, intensity and interference with behaviour (Max score= 50). A separate section quantifies the impairment caused by the tics (Max score =50).</p> |

| | |
|---|--|
| and re-admission | <p>An impact on this scale demonstrates proof of concept that electrical stimulation can reduce the severity of tics.</p> <p><i>Important to decision-making:</i></p> <p>Absolute numbers of tics can be calculated as a snapshot by performing a video evaluation of a patient according to an accepted protocol known as the Modified Rush Video rating scale (MRVRS).</p> <p>The overall impact of a patient's Tourette syndrome on their quality of life can be assessed using the Tourette syndrome quality of life scale (TSQOL).</p> <p>A common co-morbidity in Tourette patients is Obsessive Compulsive disorder. The impact of DBS on this aspect is best evaluated with the Yale Brown Obsessive Compulsive scale (YBOCS).</p> <p>Other important measures;</p> <p>Safety measures e.g. adverse events, abnormal laboratory indices.</p> <p>Evidence of treatment failure e.g. DBS resistant severe Tourette syndrome.</p> <p>Measures of cost-effectiveness e.g. incremental cost effectiveness ratio (ICER).</p> <p>Measures of unplanned health care e.g. emergency admissions</p> |
| Assumptions / limits applied to search | |
| Inclusion Criteria | <p>Articles published in English in peer reviewed journals in the last 10 years that include ADULT patients (aged 18 years and above) with severe, medication refractory Tourette syndrome (defined above).</p> <p>Given the limited number of studies that have been performed, the search should include the following: Case series, double blind evaluations and systematic reviews including but not limited to;</p> <ul style="list-style-type: none"> • Systematic review and meta-analysis • RCT • Other controlled trials, • Other uncontrolled trials, • Case series |
| Exclusion Criteria | <p>Given the paucity of information available the search should exclude reports relating to the outcomes of DBS in teenagers</p> |

| | |
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| | children <18 years. |
|--|---------------------|

1. PICO Quality assurance check list

The following criteria should be used to quality assure the PICO template prior to commissioning the evidence review:

1. Are the aims and objectives for the evidence review clearly stated?
2. Is/are the research question(s) clearly stated?
3. Do the research question(s) fully address the aims and objectives?
4. Does the PICO framework address all the issues raised in the questions

Draft for consultation

References

- ACKERMANS, L., DUIJS, A., VAN DER LINDEN, C., TIJSSEN, M., SCHRUIERS, K., TEMEL, Y., KLEIJER, M., NEDERVEEN, P., BRUGGEMAN, R., TROMP, S., VAN KRANEN-MASTENBROEK, V., KINGMA, H., CATH, D. & VISSER-VANDEWALLE, V. 2011. Double-blind clinical trial of thalamic stimulation in patients with Tourette syndrome. *Brain*, 134, 832-44.
- BALDERMANN, J. C., SCHULLER, T., HUYS, D., BECKER, I., TIMMERMANN, L., JESSEN, F., VISSER-VANDEWALLE, V. & KUHN, J. 2016. Deep Brain Stimulation for Tourette-Syndrome: A Systematic Review and Meta-Analysis. *Brain Stimulation*, 9, 296-304.
- CANNON, E., SILBURN, P., COYNE, T., O'MALEY, K., CRAWFORD, J. D. & SACHDEV, P. S. 2012. Deep brain stimulation of anteromedial globus pallidus interna for severe Tourette's syndrome. *American Journal of Psychiatry*, 169, 860-6.
- KEFALOPOULOU, Z., ZRINZO, L., JAHANSHAH, M., CANDELARIO, J., MILABO, C., BEIGI, M., AKRAM, H., HYAM, J., CLAYTON, J., KASS-ILIIYYA, L., SILVERDALE, M., EVANS, J., LIMOUSIN, P., HARIZ, M., JOYCE, E. & FOLTYNIE, T. 2015. Bilateral globus pallidus stimulation for severe Tourette's syndrome: A double-blind, randomised crossover trial. *The Lancet Neurology*, 14, 595-605.
- OKUN, M. S., FOOTE, K. D., WU, S. S., WARD, H. E., BOWERS, D., RODRIGUEZ, R. L., MALATY, I. A., GOODMAN, W. K., GILBERT, D. M., WALKER, H. C., MINK, J. W., MERRITT, S., MORISHITA, T. & SANCHEZ, J. C. 2013. A trial of scheduled deep brain stimulation for tourette syndrome: Moving away from continuous deep brain stimulation paradigms. *JAMA Neurology*, 70, 85-94.
- ROSSI, P. J., OPRI, E., SHUTE, B., MOLINA, R., BOWERS, D., WARD, H., FOOTE, D., GUNDUZ, A. & OKUN, S. 2016. Scheduled, intermittent stimulation of the thalamus reduces tics in Tourette syndrome. *Parkinsonism & Related Disorders*, 29, 35.
- SACHDEV, P. S., MOHAN, A., CANNON, E., CRAWFORD, J. D., SILBERSTEIN, P., COOK, R., COYNE, T. & SILBURN, P. A. 2014. Deep brain stimulation of the antero-medial globus pallidus interna for Tourette syndrome. *PLoS ONE*, 9 (8) (no pagination).
- WELTER, M. L., MALLET, L., HOUETO, J. L., KARACHI, C., CZERNECKI, V., CORNU, P., NAVARRO, S., PIDOUX, B., DORMONT, D., BARDINET, E., YELNIK, J., DAMIER, P. & AGID, Y. 2008. Internal pallidal and thalamic stimulation in patients with Tourette syndrome. *Archives of Neurology*, 65, 952-957.