D.6.2 Deep brain stimulation compared with best medical treatment for earlier Parkinson's disease

Bibliographic reference	Schüpbach,W.M.M., Maltete,D., Houeto,J.L., du Montcel,S.T., Mallet,L., Welter,M.L., Gargiulo,M., Behar,C., Bonnet,A.M., Czernecki,V., Pidoux,B., Navarro,S., Dormont,D., Cornu,P., Agid,Y., Neurosurgery at an earlier stage of Parkinson disease: A randomized, controlled trial, Neurology.68 (4) (pp 267-271), 2007.Date of Publication: January 2007., 267-271, 2007
Country/ies where the study was carried out	France
Study type	PILOT -RCT- full version pulished Schüpbach, Rau et al., 2013
Aim of the study	To examine whether surgery at an early stage of PD would maintain quality of life as well as improve motor function
Study dates	patient screened between 2002 and 2003 - study published 2006
Source of funding	Medtronic sponsored study
Sample size	N= 20 (n = 10 DBS, n=10 BMC)
Inclusion criteria	Inclusion criteria: • Younger than 55 years • Duration of PD 5 - 10 years • Mild to moderate motor symptoms, H&Y stage <or=3 • Motor fluctuations with off periods for >25% of the day • Normal brain MRI

Bibliographic reference	**Schüpbach,W.M.M., Maltete,D., Houeto,J.L., du Montcel,S.T., Mallet,L., Welter,M.L., Gargiulo,M., Behar,C., Bonnet,A.M., Czernecki,V., Pidoux,B., Navarro,S., Dormont,D., Cornu,P., Agid,Y., Neurosurgery at an earlier stage of Parkinson disease: A randomized, controlled trial, Neurology.68 (4) (pp 267-271), 2007.Date of Publication: January 2007., 267-271, 2007**
	• Absence of severe psychiatric disease • Absence of dementia (MDRS >130/144) • Impaired social and occupational functioning due to PD (SOFAS score 51-80%)
Exclusion criteria	Reasons for exclusion: • Absence of professional activity • Too mild disease • Abnormal brain MRI • Disease duration >10 years • Age > 55 years
Details	Patients included prospectively in pairs and randomized to surgery/medical care matched for disease duration, age, activities of daily living, motor functioning, and PD-related psychosocial situation and handicap Patients were first paired and then within each pair of patents randomization was first performed externally, with no knowledge of the patients except date of birth, into a group that would undergo surgery for bilateral STN stmulation (n = 10, 3 women), or best possible medical treatment only (n=10, 5 women) Patients ID numbers were provided by fax to the randomization centre in blocks of 2- randomized using SAS
Interventions	Sham surgery was considered unethical, therefore assessments were not blinded BMC Best medical care was individually adapted to suit each patient's motor symptoms and included: 1) A treatment with dopaminergic agonist available in Francce (pegolide ropinirole, bromocriptine, piribedil) in a dose that was well tolerated by the patient; 2) Addition of levodopa/carbidopa or levodopa/benzerazide in fluctuating patients who tolerated it well and showed benefit 3) Addition of entacapone in fluctuating patients who tolerated it well and showed benefit 4) Amantadine used as antidyskinetic in patients who tolerated it well STN DBS • Localizing procedures described elsewhere *Bejjani 2000 • Same team performed all operations • At end of study, STN stimulatioon in surgical patients was single monopolar cathodic in 9 and double monopolar cathodic on both sides in 1

<table>
<tr><th>Bibliographic reference</th><td>Schüpbach,W.M.M., Maltete,D., Houeto,J.L., du Montcel,S.T., Mallet,L., Welter,M.L., Gargiulo,M., Behar,C., Bonnet,A.M., Czernecki,V., Pidoux,B., Navarro,S., Dormont,D., Cornu,P., Agid,Y., Neurosurgery at an earlier stage of Parkinson disease: A randomized, controlled trial, Neurology.68 (4) (pp 267-271), 2007.Date of Publication: January 2007., 267-271, 2007</td></tr>
<tr><td></td><td>• Stimulation performed at 3.1 +/- 0.4V with a pulse width of 69 +/-14 and a frequency of 167 +/- 26 Hz
• All patients offered surgery after end of study
• Primary end point was relative change in overall QoL</td></tr>
<tr><td>Results</td><td>Quality of life did not change in patents in BMC but improved by 24% by end of study in those receiving STN DBS - attributed to improvement o stigmatization and bodily discomfor subdomains of assessment scale
<table>
<tr><td>Index_measure</td><td>BMC_baseline</td><td>BMC_18mnt</td><td>DBS_baseline</td><td>DBS_18mnt</td></tr>
<tr><td>PDQ39 summ index</td><td>37.9 (23.4 - 53.1)</td><td>41.9 (13.5 - 57.3)</td><td>35.4 (24.4 - 51.5)</td><td>28.9 (5.7 - 53.1)</td></tr>
<tr><td>UPDRS II (ADL)off</td><td>17.8 (6.8)</td><td>21.7 (6.3)</td><td>19.2 (7.7)</td><td>12.9 (5.7)</td></tr>
<tr><td>UPDRS II (ADL) on</td><td>3.3 (3.3)</td><td>6.3 (2.7)</td><td>2.3 (2.7)</td><td>5.1 (2.1)</td></tr>
<tr><td>MDRS</td><td>142 (137 - 144)</td><td>143 (134 - 144)</td><td>140.5 (132 - 144)</td><td>140.5 (128-144)</td></tr>
<tr><td>Frontal score</td><td>47 (38 - 50)</td><td>48.5 (31 - 50)</td><td>48 (29 - 50)</td><td>47.5 (23 - 50)</td></tr>
<tr><td>CPRS</td><td>15 (9-27)</td><td>11.5 (6 - 30)</td><td>14 (3-22)</td><td>10 (0 - 17)</td></tr>
<tr><td>MADRS</td><td>5 (0-13)</td><td>5 (2-14)</td><td>7 (0 - 12)</td><td>3 (0-9)</td></tr>
<tr><td>BAS</td><td>8 (2-11)</td><td>4 (0-9)</td><td>5 (0 - 8)</td><td>3 (0-4)</td></tr>
</table></td></tr>
<tr><td>Other information</td><td>None</td></tr>
<tr><td>Overall Risk of Bias</td><td>1. An appropriate method of randomization was used to allocate pts to treatment groups? Yes - patient randomized externally at central centre 2. There was adequate concealment of allocation: No 3. The groups were comparable at baseline, including all major confounding and prognostic factors? yes 4. Comparison groups received same care apart from interventions: Yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion? Yes 9. Groups were comparable with respect to availability of outcome data? Yes 10. Study had appropriate length of followup: yes 11. Study used a precise definition of outcome: yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: no - no blinded assessment 14. Investigators were kept blind to other important confounding and prognostic factors:no blinded assessment</td></tr>
</table>

Bibliographic reference	Schüpbach,W., Rau,J., Knudsen,K., Volkmann,J., Krack,P., Timmermann,L., Halbig,T.D., Hesekamp,H., Navarro,S.M., Meier,N., Falk,D., Mehdorn,M., Paschen,S., Maarouf,M., Barbe,M.T., Fink,G.R., Kupsch,A., Gruber,D., Schneider,G.H., Seigneuret,E., Kistner,A., Chaynes,P., Ory-Magne,F., Brefel Courbon,C., Vesper,J., Schnitzler,A., Wojtecki,L., Houeto,J.L., Bataille,B., Maltete,D., Damier,P., Raoul,S., Sixel-Doering,F., Hellwig,D., Gharabaghi,A., Kruger,R., Pinsker,M.O., Amtage,F., Regis,J.M., Witjas,T., Thobois,S., Mertens,P., Kloss,M., Hartmann,A., Oertel,W.H., Post,B., Speelman,H., Agid,Y., Schade-Brittinger,C., Deuschl,G., EARLYSTIM Study Group, Neurostimulation for Parkinson's disease with early motor complications, The New England journal of medicineN Engl J Med, 368, 610-622, 2013
Country/ies where the study was carried out	Germany and France
Study type	RCT: multicentre parallel group design comparing DBS + BSC with BSC alone (optimal medical therapy) in patients with early PD (disease duration .4yrs, H&Y <3)
Aim of the study	To assess benefit of DBS in patients with early motor complications compared to optimal medical therapy
Study dates	July 2006 to November 2009. Study published 2015.
Source of funding	German ministry of research
Sample size	N=251
Inclusion criteria	Age 18 - 60 years Disease duration > or = 4 years Disease severity rating <3 on H&Y Improvement of motor signs of 50% or more with dopaminergic medication, as assessed by UPDRS III Fluctuations or dyskinesia present for 3 years or less Score >6 ADL in the worst condition despite medical treatment (UPDRS II) Mild to moderate impairment in social and occupational functioning
Exclusion criteria	Dementia (score <or=130 on Mattis dementia) Major depression with suicidal ideation, score >25 on Beck depression inventory Disease duration < 4 years excluded because atypical forms of Parkinsonism would be expected to be identified before then
Details	Study was investigator-initiated, randomized multicentre, parallel-group design comparing DBS + BSC with medical therapy alone. Randomization performed at central coordination centre with use of randomisation lists with randomly permuted blocks lengths stratified according to centre Full source-data verification was performed by monitors from German or French coordination centers (for each country) Assessments scheduled at baseline and at 5, 12, and 24 months. Levodopa challenge test performed at baseline and 24 months

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<tr><td></td><td>Blinded assessment based on perioperative an postoperative standardized video recordings obtained at baseline and 24 months.
Videos recorded for each motor condition (according to whether patient was receiving medication or stimulation, or not).
UPDRS III assessed by 2 expert raters who were unaware of study assignment, except for assessment of rigidity, except on assessment of rigidity
During follow-up adjustments to medication and stimulation were performed according to predefined standards (EFNS)
specific procedure for monitoring risk of suicidality, established after 2 suicides had occurred during the study, consisted of baseline assessment of general risk and then semi-structured phone interview every 2 months to assess status, with psychiatric follow-up as needed.
Adverse events
All AEs reported and coded according to medical dictionary for regulatory activities (v14.1).
Serious AEs defined as any events that led to death, disability, or prolonged or new hospitalization with serious health impairment.</td></tr>
<tr><td>Interventions</td><td>Patients assigned to DBS underwent bilateral stereotactic surgery of the subthalamic nucleus with the implantation of the electrodes and pulse generator within 6 weeks after randomization. Patients then started receiving stimulation according to standards established for this study</td></tr>
<tr><td>Results</td><td>Of 392 patients assessed, 251 enrolled, n=124 DBS, n=127 BMC
Total of 25 patients had major protocol deviation: per-protocol analysis included n=116 DBS and n=110 in BMC
Baseline characteristics did not differ between treatment groups: mean:
• Age = 52 (6.3)
• Disease duration = 7.5 years (3.0)
Patients included in study after mean 1.7 years after onset of levodopa-induced motor complications of any severity
<table>
<tr><td>outcome</td><td>MD</td><td>95%CI_L</td><td>95%CI_U</td></tr>
<tr><td>PDQ39 ITT</td><td>8</td><td>4.2</td><td>11.9</td></tr>
<tr><td>PDQ39 PP</td><td>8.1</td><td>2.8</td><td>13.4</td></tr>
</table>
</td></tr>
</table>

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UPDRS III off	16.4	13.7	19.1
UPDRS II during worst cond	6.2	4.5	8
UPDRS IV	4.1	3.2	4.9
time good mobility no dys	1.9	0.4	3.4
UPDRS III off	8.6	6.4	10.9
UPDRS III on	4.5	2.7	6.4
UPDRS II best cond	0.5	-0.8	1.7
LEDD	-609.1	-662.1	-556.1
Mattis dementia	0.7	-0.6	1.9
brief pscyh rating scale	2.2	0.2	4.1
Becks depression inventory	1.9	0.3	3.6

Other information	ADVERSE EVENTS Serious AE = 123 (total N=124) in DBS and 128 in BMC (total N=127) Death by suicide = 2 in DBS and 1 in BMC. Suicide attempts, n = 2 in each group. Life-threatening event = 12 in DBS and 9 in BMC Reoperation necessary in n=4 DBS patients. intracerebral abcess or adema n = 2, dislocation of device n=5, impaired wound healing n = 4
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups? yes - patient randomized through central centre 2. There was adequate concealment of allocation: yes 3. The groups were comparable at baseline, including all major confounding and prognostic factors? yes 4. Comparison groups received same care apart from interventions: yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No - 7. All groups followed up for an equal length of time: yes 8. Groups

Bibliographic reference	Schüpbach,W., Rau,J., Knudsen,K., Volkmann,J., Krack,P., Timmermann,L., Halbig,T.D., Hesekamp,H., Navarro,S.M., Meier,N., Falk,D., Mehdorn,M., Paschen,S., Maarouf,M., Barbe,M.T., Fink,G.R., Kupsch,A., Gruber,D., Schneider,G.H., Seigneuret,E., Kistner,A., Chaynes,P., Ory-Magne,F., Brefel Courbon,C., Vesper,J., Schnitzler,A., Wojtecki,L., Houeto,J.L., Bataille,B., Maltete,D., Damier,P., Raoul,S., Sixel-Doering,F., Hellwig,D., Gharabaghi,A., Kruger,R., Pinsker,M.O., Amtage,F., Regis,J.M., Witjas,T., Thobois,S., Mertens,P., Kloss,M., Hartmann,A., Oertel,W.H., Post,B., Speelman,H., Agid,Y., Schade-Brittinger,C., Deuschl,G., EARLYSTIM Study Group, Neurostimulation for Parkinson's disease with early motor complications, The New England journal of medicineN Engl J Med, 368, 610-622, 2013
	comparable for treatmen completion? yes 9. Groups were comparable with respect to avalilability of outcome data?yes 10. Study had appropriate length of followup: yes 11. Study used a precise definition of outcome: yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention:yes, blinded assessment 14. Investigators were kept blind to other important confounding and prognostic factors: yes, blinded assessment done

Bibliographic reference	Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010
Country/ies where the study was carried out	UK
Study type	RCT: BMC vs DBS + BMC Randomized open-label trial
Aim of the study	Aimed to assess whether surgery and best medical therapy improved self-reported QoL more than therapy alone in patient's with advanced PD
Study dates	Between November 2000 and December 2006, study published 2010
Source of funding	Funding from UK medical Research council and Parkinson's UK. Birmingham university clinical trials unit received funding from the UK dept of health to cover some of costs of surgery
Sample size	N = 366, immediate DBS = 183; medical therapy alone = 183
Inclusion criteria	Patient's with PD for whom current medical therapy was not providing adequate symptomatic control were eligible. Inclusion criteria = diagnosis of PD according to UKBB criteria, age-adjusted score of >5 on dementia rating scale II (DRS II) and fitness for surgery
Exclusion criteria	None listed. Unfit for anaesthesia.
Details	Randomization

Bibliographic reference	Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010
	• Patients randomly assigned by telephone call made to central office. Allocation (1:1) to surgery and BMC or BMC alone - done by use of computerised minimisation procedure with following categoriesL age at entry (<60, 60-69, >70), years since diagnosis of PD (<5, 5-9, 10-14, >15); H&Y stage in on state (<2.0, 2.5, 3, >4), reason for considering surgery (tremor, dyskinesia, severe off periods, other reasons); type of surgery (stimulation or lesion), and region to be targeted if allocated to surgery (StN or GP pars interna) and drug therapy to be given if allocated to medical therapy (apomorphine or other std drug tmt for PD). • Pair-wise randomization option available so that centres could enter 2 patients together with one allocated to surgery and one to BMC • Patients and clinicians unmasked to treatment allocation. The local clinician selected surgical techniques and postoperative management of stimulator settings for each patient.
Interventions	DBS • Patients allocated to surgery could receive any std procedure in use at time: either stimulation or lesioning of either the StN or globus pallidus pars interna. • Surgery was to be done within 4 weeks of allocation BMC • Patients in both groups received medical therapy, which could include apomorphine according to local practice, other dopamine agonists, monoamine oxidase type B inhibitors, catechol-O-methyltransferase inhibitors, amantadine, or other drugs for treatment of Parkinson's disease symptoms. • Levodopa equivalents were calculated on the basis of 100 mg/day of standard levodopa being equivalent to the following doses of other drugs: 133 mg controlled-release levodopa; 1 mg pergolide, pramipexole, cabergoline, or rasagiline; 1·25 mg sublingual selegiline; 2 mg benzhexol; 3·3 mg rotigotine; 5 mg ropinirole; 10 mg bromocriptine, oral selegiline, or apomorphine; and 100 mg amantadine. The total levodopa dose was multiplied by 1·33 for entacapone and by 1·5 for tolcapone. • Apart from the random treatment allocation, all other aspects of the management of patients were at the discretion of the local clinicians. Patients in the medical therapy group could cross over to receive surgery after about 1 year. Assessments: • PDQ-39 - primaty outcome of interest Secondary outcomes: • UPDRS in both on and off Neurospsych assessments also done in subset of patients and involved clinical interview and battery of 16 psychometric tests and questionnaires. ** Neuropsych could not be done in all patients because trained examiners were not available in some

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<tr><td></td><td>centres. For centres that did not have trained examiners, a similar method to that used in a previous multicentre randomised controlled trial was adopted, where possible, psychologists (based on oxford) visited centres to complete assessments as required</td></tr>
<tr><td>Results</td><td>366 patients from 13 centres randomly assigned to surgery or BMC. Baseline characteristics similar. 348/366 patients were less 70yrs. 341 patients had PD for at least 5 years (mean duration 11.4 years)
5 patients in surgery group did not have surgery: 3 refused; 1 unfit for anasthesia; 1 died before surgery

<table>
<tr><td>Outcome</td><td>MD</td><td>95%CI_L</td><td>95%CI_U</td></tr>
<tr><td>UPDRS II (on)</td><td>-1</td><td>-2.4</td><td>0.4</td></tr>
<tr><td>UPDRS II off</td><td>-6.3</td><td>-8.2</td><td>-4.4</td></tr>
<tr><td>UPDRS III on</td><td>-4.5</td><td>-6.8</td><td>-2.2</td></tr>
<tr><td>UPDRS III off</td><td>-16.6</td><td>-20.4</td><td>-12.9</td></tr>
<tr><td>UPDRS IV</td><td>-4.6</td><td>-5.4</td><td>-3.7</td></tr>
<tr><td>DRS-II</td><td>0.5</td><td>-0.3</td><td>1.2</td></tr>
<tr><td>PDQ-39 (summ index)</td><td>-5.6</td><td>-8.9</td><td>-2.4</td></tr>
</table>

Adverse events:
Total serious events = 96 (in 65 people) in DBS / 29 (26 people) in BMC
NB** 12 patients in BMC group received DBS surgery between baseline and 1 year follow-up (total N in each group = 183)</td></tr>
<tr><td>Other information</td><td>Bias notes:
• Pair-wise randomization option available so that centres could enter 2 patients together with one allocated to surgery and one to BMC
• Patients and clinicians unmasked to treatment allocation.
• Neuropsych not carried out on all patients</td></tr>
</table>

Bibliographic reference	Williams,A., Gill,S., Varma,T., Jenkinson,C., Quinn,N., Mitchell,R., Scott,R., Ives,N., Rick,C., Daniels,J., Patel,S., Wheatley,K., Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): a randomised, open-label trial, The Lancet Neurology.9 (6) (pp 581-591), 2010.Date of Publication: June 2010., 581-591, 2010
	• Targets and methods (stimulation or lesion) left to individual clinician - no control! NB: Authors confirm that all patients had stimulation - no lesioning was carried out.
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - Pair-wise randomization option available so that centres could enter two patients together 2. There was adequate concealment of allocation: No 3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes 4. Comparison groups received same care apart from interventions: No - those in surgical condition attended significantly more follow-up appointments with PD nurses and clinical team than those in medical care 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion: Yes 9. Groups were comparable with respect to avalilability of outcome data: Yes 10. Study had appropriate length of follow-up: Yes 11. Study used a precise definition of outcome: Yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: Yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: No 14. Investigators were kept blind to other important confounding and prognostic factors:unclear Serious risk of bias: No blinding was carried out, patients in surgical condition recieved significantly more medical attention in the form of clinic and follow-up appointments than those in best medical care arm.

Bibliographic reference	Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014
Full citation	Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna,

Bibliographic reference	**Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014**
	Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014
Ref Id	675550
Country/ies where the study was carried out	USA
Study type	Pilot RCT: prospective, randomised, parallel-group, single-blind trial
Aim of the study	To investigate the preliminary safety and tolerability of DBS in early PD
Study dates	August 2006 - April 2009
Source of funding	Medtronic, Inc, National Centre for Advancing Translational Sciences (NCATS), NCATS/NIH award, and by private donations.
Sample size	N=30 (n=15 ODT, n=15 DBS+ODT)
Inclusion criteria	• Idiopathic PD (Hoehn & Yahr Stage II off medication) • Age 50-75 • On medication ≥6 months but <4 years • Absence of motor fluctuations or dyskinesias • MRI within normal range for age • Demonstrated response to dopaminergic therapy
Exclusion criteria	• Subjects younger than 50 years of age • Evidence of an alternative diagnosis or secondary parkinsonism • Uncontrolled medical condition or clinically significant medical disease that would increase the risk of developing pre- or postoperative complications • Evidence of dementia • Major psychiatric disorders • Previous brain operation or injury • Active participation in another clinical trial for the treatment of PD

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<tr><td></td><td>Patients with demand cardiac pacemakers or medical conditions that require repeat MRI scans
Evidence of existing dyskinesias or motor fluctuations</td></tr>
<tr><td>Details</td><td>Prior to randomisation, included patients were scheduled for an 8 day inpatient baseline assessment, which included a 7 day medication washout. Details on the method of randomisation were reported elsewhere.</td></tr>
<tr><td>Interventions</td><td>All subjects randomised to DBS+ODT were implanted in three stages using the same methodology used as standard of care at Vanderbilt University Medical Centre
Four weeks after lead implantation, subjects presented off medication for at least 36 hours for evaluation of the clinical response to stimulation
Programming was performed in a standardised fashion using the same methods used for patients with advanced PD
Pulse width was fixed at 60µsec and frequency at 130 Hz.
Modest stimulation increases were performed over three subsequent visits within 6 months based on clinical response.
Primary endpoint was the time to reach a 4-point worsening from baseline in the UPDRS III following a one week treatment washout</td></tr>
<tr><td>Results</td><td>Baseline characteristics did not differ between treatment groups.
In total 30 patients were included in the study, 1 withdrew from the ODT group after baseline due to family and financial circumstances and was therefore not included in the final analysis.
Two SAEs were reported in the DBS+ODT group: 1 patient suffered from perioperative stroke and 1 suffered from lead infection and the device was subsequently removed.
Mean change scores from baseline to 24 months (ODT n=14, DBS+ODT n=15). All on assessments were completed on Day 1 of the washout with subjects on medicine and stimulation, if applicable. All off assessments were completed on Day 8 with subjects off medicine and stimulation if applicable:
<table>
<tr><td>Outcome</td><td>MD (95% CI)</td></tr>
<tr><td>UPDRS II on</td><td>1.8 (-3.1 to 6.7)</td></tr>
<tr><td>UPDRS II off</td><td>-1.2 (-6.1 to 3.7)</td></tr>
<tr><td>UPDRS III* on</td><td>-3.4 (-12.1 to 5.4)</td></tr>
<tr><td>UPDRS III* off</td><td>-1.37 (-9.6 to 6.9)</td></tr>
</table></td></tr>
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Bibliographic reference	**Charles,David, Konrad,Peter E., Neimat,Joseph S., Molinari,Anna L., Tramontana,Michael G., Finder,Stuart G., Gill,Chandler E., Bliton,Mark J., Kao,Chris C., Phibbs,Fenna T., Hedera,Peter, Salomon,Ronald M., Cannard,Kevin R., Wang,Lily, Song,Yanna, Davis,Thomas L., Subthalamic Nucleus Deep Brain Stimulation in Early Stage ParkinsonGÇÖs Disease, Parkinsonism & related disordersParkinsonism Relat Disord, 20, 731-737, 2014**
	<table><tr><td>UPDRS IV</td><td>-1.59 (-3.7 to 0.5)</td></tr><tr><td>UPDRS Total*</td><td>-2.7 (-14.7 to 9.3)</td></tr></table> *Rigidity was not included in the UPDRS III scores
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups? Unclear 2. There was adequate concealment of allocation: Unclear 3. The groups were comparable at baseline, including all major confounding and prognostic factors? Yes 4. Comparison groups received same care apart from interventions: Yes 5. Pts receiving care were kept blind to tmt allocation: No - not possible 6. Individuals administering care were kept blind to tmt allocation: No 7. All groups followed up for an equal length of time: Yes 8. Groups comparable for treatment completion? Yes 9. Groups were comparable with respect to availability of outcome data? Yes 10. Study had appropriate length of followup: Yes 11. Study used a precise definition of outcome: yes - clearly defined outcomes 12. Valid and reliable method was used to determine the outcome: yes - well-validated measures used 13. Investigators were kept blind to participants exposure to the intervention: Rater blinded to UPDRS III outcome only 14. Investigators were kept blind to other important confounding and prognostic factors: Unclear