D.6 Advanced therapies: deep brain stimulation and levodopa–carbidopa intestinal gel

D.6.1 Brain stimulation, levodopa–carbidopa intestinal gel and best medical treatment for advanced Parkinson's disease

DBS -v- BMT

Bibliographic reference	**Deuschl,G., Schade-Brittinger,C., Krack,P., Volkmann,J., Schafer,H., Botzel,K., Daniels,C., Deutschlander,A., Dillmann,U., Eisner,W., Gruber,D., Hamel,W., Herzog,J., Hilker,R., Klebe,S., Kloss,M., Koy,J., Krause,M., Kupsch,A., Lorenz,D., Lorenzl,S., Mehdorn,H.M., Moringlane,J.R., Oertel,W., Pinsker,M.O., Reichmann,H., Reuss,A., Schneider,G.H., Schnitzler,A., Steude,U., Sturm,V., Timmermann,L., Tronnier,V., Trottenberg,T., Wojtecki,L., Wolf,E., Poewe,W., Voges,J., German Parkinson Study Group,Neurostimulation Section, 20060905, A randomized trial of deep-brain stimulation for Parkinson's disease.[Erratum appears in N Engl J Med. 2006 Sep 21;355(12):1289], New England Journal of Medicine, 355, 896-908, 2006**
Country/ies where the study was carried out	Germany and Austria (10 centres)
Study type	RCT of DBS for PD compared to best medical management
Aim of the study	Changes in the quality of life and motor function, the latter assessed while the patient was not receiving medication, were the primary outcomes
Study dates	No dates given, published 2006
Source of funding	Supported by a grant from the German Federal Ministry of Education and Research.
Sample size	N = 156 (78 per arm)
Inclusion criteria	Patients were eligible for enrolment if they: • had received a clinical diagnosis of idiopathic Parkinson's disease according to the British Parkinson's Disease Society Brain Bank criteria at least five years previously; • were under 75 years of age;

<table>
<tr><th>Bibliographic reference</th><td>Deuschl,G., Schade-Brittinger,C., Krack,P., Volkmann,J., Schafer,H., Botzel,K., Daniels,C., Deutschlander,A., Dillmann,U., Eisner,W., Gruber,D., Hamel,W., Herzog,J., Hilker,R., Klebe,S., Kloss,M., Koy,J., Krause,M., Kupsch,A., Lorenz,D., Lorenzl,S., Mehdorn,H.M., Moringlane,J.R., Oertel,W., Pinsker,M.O., Reichmann,H., Reuss,A., Schneider,G.H., Schnitzler,A., Steude,U., Sturm,V., Timmermann,L., Tronnier,V., Trottenberg,T., Wojtecki,L., Wolf,E., Poewe,W., Voges,J., German Parkinson Study Group,Neurostimulation Section, 20060905, A randomized trial of deep-brain stimulation for Parkinson's disease.[Erratum appears in N Engl J Med. 2006 Sep 21;355(12):1289], New England Journal of Medicine, 355, 896-908, 2006</td></tr>
<tr><td></td><td>• had parkinsonian motor symptoms or dyskinesias that limited their ability to perform the activities of daily living, despite receipt of optimal medical therapy;
• had no dementia or major psychiatric illness and
• had no contraindications to surgery
Neurologists specializing in movement disorders at the participating centres gave their assurance that each patient had received state-of-the-art antiparkinsonian medication.</td></tr>
<tr><td>Exclusion criteria</td><td>See inclusion criteria</td></tr>
<tr><td>Details</td><td>Centres enrolled patients in pairs, with one randomly assigned to neurostimulation within six weeks and the other to best medical treatment
Randomisation, monitoring and data management were performed by the Coordinating Centre for Clinical Trials at Philipps University, Marburg, Germany</td></tr>
<tr><td>Interventions</td><td>Intervention: Bilateral stereotactic surgery under local anaesthesia. The STN was targeted by MRI, ventriculography, microelectrode recording or a combination of these (varied by centre). Kinetra Medtronic implants used.
Standard pulse setting was 60µsec in duration at 130Hz, with voltage adjusted to the individual patient
Best medical treatment - individualised optimal drug therapy according to the guidelines of the German Society of Neurology. Drugs adjusted to patient need throughout the study</td></tr>
<tr><td>Results</td><td>Demographics:
• Mean age = 60.7 (7.6)
• Disease duration = 13.4 years (5.7)
• Female = 56 /156 (36%)
Results:
<table>
<tr><td>index_measure</td><td>DBS_baseline</td><td>BMC_baseline</td><td>DBS_6mnt</td><td>BMC_6mnt</td><td>DBS_change</td><td>BMC_ change</td></tr>
<tr><td>PDQ-39 index</td><td>41.8 (13.9)</td><td>39.6 (SD 16.0)</td><td>31.8 (SD 16.3)</td><td>40.2 (SD 14.4)</td><td>9.5 (5.9, 13.1)</td><td>-0.2 (-2.9, 2.4)</td></tr>
<tr><td>UPDRS III off</td><td>48.0 (SD 12.3)</td><td>46.8 (SD 12.1)</td><td>28.3 (SD 14.7)</td><td>46.0 (SD 12.6)</td><td>19.6 (16.1, 23.2)</td><td>0.4 (-1.8, 2.6)</td></tr>
<tr><td>UPDRS III on</td><td>18.9 (SD 9.3)</td><td>17.3 (SD 9.6)</td><td>14.6 (SD 8.5)</td><td>17.85 (SD 10.6)</td><td>4.0 (1.7, 6.4)</td><td>-0.4 (-2.2, 1.4)</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Deuschl,G., Schade-Brittinger,C., Krack,P., Volkmann,J., Schafer,H., Botzel,K., Daniels,C., Deutschlander,A., Dillmann,U., Eisner,W., Gruber,D., Hamel,W., Herzog,J., Hilker,R., Klebe,S., Kloss,M., Koy,J., Krause,M., Kupsch,A., Lorenz,D., Lorenzl,S., Mehdorn,H.M., Moringlane,J.R., Oertel,W., Pinsker,M.O., Reichmann,H., Reuss,A., Schneider,G.H., Schnitzler,A., Steude,U., Sturm,V., Timmermann,L., Tronnier,V., Trottenberg,T., Wojtecki,L., Wolf,E., Poewe,W., Voges,J., German Parkinson Study Group,Neurostimulation Section, 20060905, A randomized trial of deep-brain stimulation for Parkinson's disease.[Erratum appears in N Engl J Med. 2006 Sep 21;355(12):1289], New England Journal of Medicine, 355, 896-908, 2006						
	UPDRS II off	22.5 (SD 7.2)	21.9 (SD 6.4)	13.7 (SD 7.9)	22.9 (SD 5.7)	8.8 (6.8, 10.8)	-0.8 (-2.3, 0.7)
	UPDRS II on	9.0 (SD 5.5)	7.9 (SD 5.8)	7.6 (SD 5.4)	9.0 (SD 5.3)	1.5 (0.2, 2.7)	-1.1 (-2.3, 0.1)
	Dyskinesia off	0.5 (SD 2.0)	0.5 (SD 1.7)	0.2 (SD 1.7)	0.1 (SD 0.6)	0.2 (-0.4, 0.7)	0.2 (-0.2, 0.6)
	Dyskinesia on	6.7 (SD 5.3)	8.4 (SD 5.9)	3.1 (SD 3.5)	8.6 (SD 5.5)	3.4 (2.3, 4.5)	-0.4 (-1.5, 0.7)*
	SES off	47 (SD 19)	48 (SD 19)	70 (SD 20)	45 (SD 18)	-23 (-28, 18)	1 (-2, 5)
	SES on	80 (SD 19)	82 (SD 17)	83 (SD 16)	79 (SD 15)	-4 (-7, 0)	3 (0, 7)
	Ldopa (mg/day)	1176 (SD 517)	1175 (SD 461)	597 (SD 381)	1060 (SD 467)	-593 (-722, -463)*	-95 (-187, -3)*
	MDRS	139.6 (SD 3.8)	140.3 (SD 3.4)	137.5 (SD 5.7)	139.6 (SD 4.7)	2.0 (0.8, 3.2)	0.5 (-0.5, 1.5)
	MADRS	8.5 (SD 5.5)	7.7 (SD 5.8)	8.1 (SD 6.6)	8.5 (SD 5.4)	0.3 (-1.5, 2.1)	-0.6 (-2.1, 0.9)
	BPRS	27.7 (SD 5.2)	27.1 (SD 6.2)	24.8 (SD 5.3)	26.4 (SD 5.3)	2.7 (1.0, 4.4)	0.8 (-0.7, 2.3)
	*sign corrected from paper						
Other information	None						
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - patient randomized externally in pairs 2. There was adequate concealment of allocation: Unclear 3. The groups were comparable at baseline, including all major confounding and prognostic factors: Yes - matched pairs randomized 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						

Bibliographic reference	**Deuschl,G., Schade-Brittinger,C., Krack,P., Volkmann,J., Schafer,H., Botzel,K., Daniels,C., Deutschlander,A., Dillmann,U., Eisner,W., Gruber,D., Hamel,W., Herzog,J., Hilker,R., Klebe,S., Kloss,M., Koy,J., Krause,M., Kupsch,A., Lorenz,D., Lorenzl,S., Mehdorn,H.M., Moringlane,J.R., Oertel,W., Pinsker,M.O., Reichmann,H., Reuss,A., Schneider,G.H., Schnitzler,A., Steude,U., Sturm,V., Timmermann,L., Tronnier,V., Trottenberg,T., Wojtecki,L., Wolf,E., Poewe,W., Voges,J., German Parkinson Study Group,Neurostimulation Section, 20060905, A randomized trial of deep-brain stimulation for Parkinson's disease.[Erratum appears in N Engl J Med. 2006 Sep 21;355(12):1289], New England Journal of Medicine, 355, 896-908, 2006**
	9. Groups were comparable with respect to availability of outcome data: Yes 10. Study had appropriate length of follow-up: Yes - further follow up reported in Witt et al., 2013 paper 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: Investigators initially kept blind to patient details but intervention group known (surgical scars obvious)

Bibliographic reference	**Okun,M.S., Gallo,B.V., Mandybur,G., Jagid,J., Foote,K.D., Revilla,F.J., Alterman,R., Jankovic,J., Simpson,R., Junn,F., Verhagen,L., Arle,J.E., Ford,B., Goodman,R.R., Stewart,R.M., Horn,S., Baltuch,G.H., Kopell,B.H., Marshall,F., Peichel,P., Pahwo,R., Lyons,K.E.,Trster,A.I., Vitek,J.L., Tagliati,M., for the SJM DBS Study Group., Subthalmic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, The Lancet Neurology. 11 (pp140-149), 2012. Date of Publication: 11 January 2012**
Country/ies where the study was carried out	USA
Study type	Randomised controlled open-label study
Aim of the study	To assess the safety and efficacy of bilateral constant-current DBS of the subthalmic nucleus.
Study dates	September 2005 – August 2010
Source of funding	St Jude Medical Neuromodulation division (Note: all authors have multiple conflicts of interests with a range of research and pharmaceutical companies)
Sample size	N = 136; n immediate DBS = 101, n delayed DBS = 35
Inclusion criteria	• Adults aged 18-80 years of age • Diagnosed with Parkinson's disease (UK Parkinson's Disease Society Brain Bank criteria) for at least 5 years • At least 6 hours daily "off-time" or moderate to severe dyskinesias during waking hours • A history of improvement of Parkinson's symptoms of levodopa therapy

Bibliographic reference	**Okun,M.S., Gallo,B.V., Mandybur,G., Jagid,J., Foote,K.D., Revilla,F.J., Alterman,R., Jankovic,J., Simpson,R., Junn,F., Verhagen,L., Arle,J.E., Ford,B., Goodman,R.R., Stewart,R.M., Horn,S., Baltuch,G.H., Kopell,B.H., Marshall,F., Peichel,P., Pahwo,R., Lyons,K.E.,Trster,A.I., Vitek,J.L., Tagliati,M., for the SJM DBS Study Group., Subthalmic deep brain stimulation with a constant-current device in Parkinson's disease: an open-label randomised controlled trial, The Lancet Neurology. 11 (pp140-149), 2012. Date of Publication: 11 January 2012**
	• Willing to maintain a constant dose of anti-Parkinson's disease medication for at least one month prior to study enrolment • Available for appropriate follow-up times for the length of the study
Exclusion criteria	• Any major illness or medical condition that would interfere with participation in the study • Currently suffers from untreated, major depression • An electrical or electromagnetic implant (e.g. cochlear prosthesis or pacemaker) • A prior surgery for the treatment of PD symptoms, including previous DBS surgery • Dementia • Drug or alcohol abuse • Woman of child-bearing potential • History of seizures
Details	Patients randomly assigned to either immediate DBS or 3-month delayed stimulation The randomisation ratio was 3:1, to maximise the number of patients exposed to stimulation Randomisation was computer-generated (SAS version 9.2) in blocks of four at each site before the start of the trial Patients and raters were aware of group assignment after device implantation
Interventions	Bilateral lead implantations were done either in one surgery (simultaneous bilateral implantation) or in a staged procedure with the two lead implantations separated by 2–4 weeks DBS devices (Libra DBS device) were implanted by use of MRI or CT-MRI fusion for targeting and microelectrode recording for target refinement, followed by intra- operative test stimulation of the DBS lead. The pulse generators were placed in a subclavicular position either on the same day or within a maximum of 6 weeks of lead implantation. All participating centres used microelectrode recording to refine targeting and DBS placement All participating centres used existing DBS surgery equipment and were asked to physiologically refine the DBS targets based on their best medical practices. Devices implanted into patients in the stimulation group were programmed within 7 days after surgical implantation (day 0); those in the control group were not programmed until 3 months after implantation (day 90). Statistical analyses The analysis of the primary outcome was based on the difference between groups (stimulation vs control) in the duration of on time measured by patients' diaries at 3 months. This change was done by a two-way analysis of covariance that included the

<table>
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<tr><td></td><td>effects of treatment, study centre, and good quality on time at baseline. Study centres with fewer than four patients (n=2) were pooled to create a composite centre. Treatment effect was tested by a two-sided test at a significance level of 5%.</td></tr>
<tr><td>Results</td><td>Demographics:

<table>
<tr><td>Characteristic</td><td>Stimulation group (n=101)</td><td>Control group (n=35)</td></tr>
<tr><td>Age (years)</td><td>60.6 (SD 8.3)</td><td>59.5 (SD 8.2)</td></tr>
<tr><td>% Male</td><td>62%</td><td>60%</td></tr>
<tr><td>Disease duration (years)</td><td>12.1 (SD 4.9)</td><td>11.7 (SD 4.1)</td></tr>
<tr><td>% White</td><td>90</td><td>89</td></tr>
<tr><td>% African-American</td><td>1</td><td>0</td></tr>
<tr><td>% Hispanic</td><td>8</td><td>9</td></tr>
<tr><td>% Other ethnic origin</td><td>1</td><td>3</td></tr>
<tr><td>Weight (kg)</td><td>80.6 (SD 18.3)</td><td>74.8 (SD 15.6)</td></tr>
<tr><td>Height (cm)</td><td>173.5 (SD 11.2)</td><td>171.2 (SD 10.4)</td></tr>
</table>

Efficacy analysis
<table>
<tr><td>Measure</td><td>Intervention (baseline)</td><td>Control (baseline)</td><td>Intervention (3m)</td><td>Control (3m)</td><td>Intervention (change)*</td><td>Control (change)*</td><td>Difference in change (95% CI)</td></tr>
<tr><td>Good quality on time</td><td>6.7 (SD 3.1)</td><td>7.4 (SD 2.5)</td><td>11.2 (SD 4.5)</td><td>8.9 (SD 2.9)</td><td>4.27</td><td>1.77</td><td>2.25 (0.87, 4.16)</td></tr>
<tr><td>UPDRS on</td><td>39.6 (SD 13.0)</td><td>38.6 (SD 14.4)</td><td>32.7 (SD 14.8)</td><td>44.6 (SD 13.6)</td><td>-6.83</td><td>5.33</td><td>-12.2 (-17.3, -7.0)</td></tr>
</table>
</td></tr>
</table>

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	UPDRS 1 on	1.97 (SD 1.88)	1.77 (SD 1.69)	2.02 SD 91.87)	1.97 (SD 1.51)	0.17	0.18	0.00 (-0.68, 0.68)
	UPDRS 2 on	9.2 (SD 5.6)	9.9 (SD 6.3)	10.3 (SD 6.5)	11.7 (SD 7.2)	1.02	1.93	-0.91 (-3.43, 1.61)
	UPDRS 3 off1	40.8 (SD 10.8)	44.1 (SD 14.0)	38.5 (SD 13.4)	40.4 (SD 11.6)	-1.97	-2.56	0.59 (-3.06, 4.24)
	UPDRS 3 off2	40.8 (SD 10.8)	44.1 (SD 14.0)	24.8 (SD 10.1)	40.4 (SD 11.6)	-16.1	-2.1	-14.0 (-17.5, -10.5)
	UPDRS 3 on	18.3 (SD 9.5)	17.8 (SD 10.1)	15.1 (SD 8.2)	22.3 (SD 10.5)	-3.01	4.37	-7.38 (-10.18, -4.57)
	UPDRS 4 on	8.8 (SD 3.5)	9.6 (SD 3.6)	4.5 (SD 2.9)	8.0 (SD 4.1)	-4.40	-1.00	-3.41 (-4.62, -2.19)
	Ldopa dose (mg)	1311 (SD 615)	1459 (SD 991)	864 (SD 551)	1272 (SD 608)	-492	-131	-361 (-529, -193)
	SES on	77.6 (SD 16.8)	76.5 (SD 16.3)	86.1 (SD 11.4)	76.8 (SD 17.7)	8.8	-0.5	9.3 (4.4, 15.3)
	HDI	66.1 (SD 13.2)	69.3 (SD13.7)	57.4 (SD 13.7)	66.2 (SD 11.9)	-9.14	-1.80	-7.34 (-12.37, -2.31)
	D-KEFS	10.6 (SD 3.8)	9.9 (SD 3.6)	8.7 (SD 3.6)	8.6 (SD 3.6)	-1.90	-1.52	-0.38 (-1.39, 0.63)
	Hoehn and Yahr off	2.94 (SD 0.80)	3.30 (SD 0.89)	2.38 (SD 0.07)	3.14 (SD 0.95)	-0.64	-0.07	-0.57 (-0.81, -0.32)
	*Adjusted for study site and baseline. [1]Comparison of baseline off medication with 3 months stimulation off and medication off. [2]Comparison of baseline off medication with 3 months stimulation on and medication off							

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Other information

Adverse events	Stimulation (0-3m)		Control (0-3m)		All patients (3-12m)	
	No events (%)	No patients (%)	No events (%)	No patients (%)	No events (%)	No patients (%)
All SAEs (n=50)	20 (40)	14 (14)	7 (14)	4 (11)	23 (46)	23 (17)
Confusion	1 (2)	1 (1)	0	0	0	0
CSF leakage	1 (2)	1 (1)	0	0	0	0
Depression	0	0	0	0	1 (2)	1 (<1)
Erosion through skin	0	0	0	0	1 (2)	1 (<1)
Gait disorder	1 (2)	1 (1)	0	0	3 (6)	3 (2)
Hardware problem (lead)	1 (2)	1 (1)	0	0	0	0
Infection	3 (6)	2 (2)	1 (2)	1 (3)	2 (4)	2 (1)
ICH	3 (6)	3 (3)	1 (2)	1 (3)	0	0
Lead migration	2 (4)	2 (2)	0	0	0	0
Loss of stimulation	0	0	0	0	1 (2)	1 (<1)
Motor fluctuations	1 (2)	1 (1)	0	0	0	0
Worsening of PD	1 (2)	1 (1)	1 (2)	1 (3)	1 (2)	1 (<1)
Pneumonia	0	0	1 (2)	1 (3)	0	0
Psychiatric disturbances	0	0	0	0	1 (2)	1(<1)
Seizures or convulsions	1 (2)	1 (1)	0	0	0	0

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	Tremor	1 (2)	1 (1)	0	0	0	0
	Unrelated events	4 (8)	3 (3)	3 (6)	2 (6)	13 (26)	13 (10)
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes 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 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 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: Yes						

Bibliographic reference	Perestelo-Perez,L., Rivero-Santana,A., Perez-Ramos,J., Serrano-Perez,P., Panetta,J., Hilarion,P., Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials, Journal of NeurologyJ Neurol, 261, 2051-2060, 2014
Country/ies where the study was carried out	Spain
Study type	Meta-analysis: 6 x RCTs of DBS vs BSC
Aim of the study	To perform a a systematic analysis and to evaluate the efficacy of DBS to improve motor signs, functionality, and quality of life in PD patients
Study dates	Published 2014

Bibliographic reference	**Perestelo-Perez,L., Rivero-Santana,A., Perez-Ramos,J., Serrano-Perez,P., Panetta,J., Hilarion,P., Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials, Journal of NeurologyJ Neurol, 261, 2051-2060, 2014**
Source of funding	Spanish health ministry
Sample size	6 RCT's, N = 1,184
Inclusion criteria	RCT's that compared DBS plus medication vs medication (alone or + sham device) in PD patients
Exclusion criteria	None listed.
Details	The following databases consulted up to April 2013: Medline, PreMedline, EMBASE, PsychInfo, CINAHL, Cochrane library, and center for reviews & dissemination Search strategy developed for each database using a combination of medical subject heading and free text terms: deep brain stimulation, electic stimulation therapy, DBS, bilateral DBS, cortical stimulation, brain pacemaker, neurostimulat [brain, cerebral, cingulate, cinguli, capsule, striatum, accumbens, thalam, cortex, hebenula, subthalamic nucleaus, STN, excitation, stimul, deep, depth, electric] Outcome measures of interest were: motor function (UPDRS III), waking time on good function without troubling dyskinesia, LEDD reduction, medication-induced complications, ADL, HRQoL, neurocognitive, psychiatric effects. 2 review authors screened all reporws of RCT;s and 5 extacted data independently. Resolved inconsistencies by discussion consensus Risk of bias done according to Cochrane criteria for judging risk of bias. Risk of bias assessed by 2 review authors indepdendently
Interventions	Deep brain stimulation: in all cases, an electrode was bilaterally implanted in the STN, except for 1/2 of intervention group in Weaver et al, and 4 participants in Williams et al., who received surgery in globus pallidus interna (GPi)
Results	Demographics Mean age 60, except in Shupbach (recruited early disease) where mean ages for both studies were 48 and 52 years Follow up time ranged from 3 months to 24 months. None of the studies were sham-controlled. Okun et al., controlled for implantation effect since all patients underwent the surgical procedure. Randomized-pairs design was applied by 2 studies, whereas in another study, (PDSURG) this was left to participating centers. Randomization method explicitly reported in 4 studies and allocation concealment described in 2 studies Motor function assessments conducted by blind raters only in 2 studies Participants lost to follow-up were approximately 14% in one study and <10% in the remaining studies Main outcomes:

Outcome	K	n	MD	95%_L	95%_U	Het I2

Bibliographic reference	**Perestelo-Perez,L., Rivero-Santana,A., Perez-Ramos,J., Serrano-Perez,P., Panetta,J., Hilarion,P., Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials, Journal of NeurologyJ Neurol, 261, 2051-2060, 2014**

UPDS III off	5	1001	15.2	12.23	18.18	77
UPDRS III on	5	1018	4.36	2.8	5.92	54
Time on w/o troublesome dyskinesia	4	719	3.25	1.78	4.71	75
ldopa recuction mg/d	4	759	452.31	288.48	616.14	87
Med induced complication (UPDRS IV)	4	820	3.67	3.03	4.31	48
ADL off (UPDRS II)	4	641	7.39	5.65	9.12	55
ADL on (UPDRS II)	6	1041	1.77	0.11	3.44	82
PDQ-39	5	980	7.43	5.61	9.26	25
UPDRS I	5	1029	0.29	0.05	0.35	0

Significant effect of DBS on:

- UPDRS III off and on states (15.2 and 4.36 points, respectively)
- waking time without troublesome dyskinesia (3.25 hrs)
- LEDD dose (452.3 mg/d)
- med-induced complications (3.67 points
- ADL off (7.39 points)
- ADL on (1.77 points)
- PDQ-39 (7.43 points)
- Neurocognitive effects - 5 studies applied UPDRS 1 (mood mental status, behavioural problems). Significant result favored DBS (0.29, 95%CI: 0.06, 0.53)

Outcomes in favor of medication group (i.e. worse in DBS)

4 studies assessed dementia (Mattis dementia scale) significant result in favor medication group (MD = -1.01, 95%CI = -1.74, -0.28)

4 studies assessed semantic fluency, 3 verbal fluency. Both worse in DBS group: (SMD = -0.34, 95%CI: -0.52, -0.16) verbal(SMD = -0.56, 95%CI: -0.73, -0.38)

2 studies assessed verbal and visuospatial memory. No statistically significant differences observed

Bibliographic reference	**Perestelo-Perez,L., Rivero-Santana,A., Perez-Ramos,J., Serrano-Perez,P., Panetta,J., Hilarion,P., Deep brain stimulation in Parkinson's disease: meta-analysis of randomized controlled trials, Journal of NeurologyJ Neurol, 261, 2051-2060, 2014**
	same studies assessed stroop, worse in DBS (SMD = -0.26, 95%CI: -0.47, -0.06) Psychiatric effects: 2 studies used brief psychiatric rating scale to assess mental health: statistically in favor of DBS (MD = 2.07, 0.61 to 3.53) 3 studies examined depressionwith Montgomery Asberg depression rating scale (MADRS) - signifiacntly in favor of DBS (MD = 2.00, 95%CI: 0.69, 3.30) Conclusions: Results show DBS is an effecive treatment to control patients symptoms and improve functionality and quality of life
Other information	None
Overall Risk of Bias	NICE meta-analysis quality checklist: • The review address an appropriate and clearly focused question is relevant to the guideline review question: Yes - clearly focused review question that matches review question defined in present review protocol. • The review collects the type of studies you consider to the question review question: Yes - all relevant studies are assessed by the review. • The literature search sufficient rigorous to identify all the relevant studies: Yes - Literature search was sufficiently and almost replicates that carried out by NICE. The following databases were searched: MEDLINE, Pre-Medline, EMBASE, PsycInfo, CINAHL, Cochrane Library and centre for reviews and dissemination. • Study quality is assessed and reported: Yes - study quality assessed for each of the RCTs according to the Cochrane criteria for risk of bias. • An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes - review performed in accordance with PRISMA statement which provides structured advice on reporting style. Methods for the review are detailed and all relevant methodologies for each of the RCT's are detailed within the paper.

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
Country/ies where the study was carried out	USA

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
Study type	RCT
Aim of the study	To compare 6 month outcomes of patients who received DBS or best medical care (BMC)
Study dates	Patients recruited between May 2002 and Oct 2005. Study published Feb 2010.
Source of funding	The Cooperative Studies Program of the Department of Veterans Affairs Office of Research and Development, the National Institute of Neurological Disorders and Stroke, and Medtronic Neuromodulation provided financial support for this study.
Sample size	N= 255 : DBS StN n=60, DBS GP = 61, BMC = 134
Inclusion criteria	Patients with ideopathic PD were eligible if they • Were classified as H&Y stage 2 or greater while not taking medication • Were responsive to levodopa • Had persistent disabling symptoms (e.g. motor fluctuations, dyskinesia) • Experienced 3 + hrs per 24hr period with poor motor function or symptom control • Were receiving stable medical therapy for 1 month or greater, and • Were aged 21 or older. • Patients were not required to have a caregiver. • Further requirement: 3hr off time and/or on time with troubling dyskinesia per day eligibility criteria
Exclusion criteria	• Atypical syndromes • Previous surgery for PD • Surgical contraindications • Active alcohol or drug abuse • Dementia (MMSE <25), or • Pregnancy
Details	Randomization • Randomization to DBS or BMC included stratification by study site and patient age (<70 vs > 70). Motor function assessments were conducted by raters blinded to treatment Study procedure • Recruitment included referrals to neurologists and patient self-referrals. study sites were Seven Veterans Affairs and 6 affiliated university medical centres.

Bibliographic reference	Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009
	• Study sites were selected on a competitive basis and required the participation of a movement disorder neurologist, a surgeon with expertise in globus pallidus and subthalamic nucleus deep brain stimulation implants and microelectrode recording, and appropriate supportive services (e.g., neuropsychologists). • Patients arrived at clinic having stopped their medications the night before. UPDRS motor subscale conducted in 'off state' by neurologist. A second, blinded neurologist independently completed motor subscale. All patients wore caps during assessment to ensure blinding from craniotomy scars. • Patients took their medications and were assessed 1 hour later in 'on' state. - H&Y, stand-walk-sit test, UPDRS subscales, PDQ-39. Nurse recorded medications and physical health status and PD status • Neurocognitive test battery undertaken - Mattis dementia rating scale, tests of attention, working memory, visuomotor speed, WASI III, verbal fluency, Stroop, card sorting, Boston naming test, verbal learning test, manual tapping speed, and mood. • Patients completed diaries and recorded which of 4 categories (on, on with troubling dyskinesia, off, or asleep) best reflected their predominant functioning for the prior 30mins in 30min intervals for 2 days to determine study eligibility. Patients unaware of 3hr off time and/or on time with troubling dyskinesia per day eligibility criteria when completing diaries. Follow up: • Patients returned to their study site at 3 and 6 months • Abbreviated motor function and quality-of-life assessments were conducted at 3 months. The entire baseline assessment was repeated at 6 months. • Study neurologists and blinded neurologists independently assessed patients' UPDRS motor scores while patients were not taking medication. • Patients receiving deep brain stimulation kept their stimulators on for the first assessment, then had them deactivated for return 1 hour later for assessment off medication, off stimulation. • Patients receiving best medical therapy remained off medication and returned for a second assessment to equalize assessments in each group. After the second assessment, the deep brain stimulation systems were reactivated. All patients took their medications and returned 1 hour later for a third blinded and unblinded assessment. • Patients completed the remaining assessments, including the UPDRS and neurocognitive tests, while taking medication. Statistical analysis • Analyses were based on the intent-to-treat principle. For patients with at least 1 follow-up visit but incomplete follow-up, the last observation was carried forward and treated as the 6-month observation.

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	• For patients without baseline data, follow-up data, or both, the change score was set to zero. A second analysis excluded those without follow-up or baseline data. The primary outcome was the baseline to 6-month change in time spent in the on state without troubling dyskinesia. • The mean group change was compared between treatment groups using a 2-sample t test. Secondary outcomes were measured as baseline to 6-month changes. • Medication usage was converted to levodopa equivalents for analysis
Interventions	Patients who received deep brain stimulation were further randomized to subthalamic nucleus or globus pallidus targets and underwent surgery within 1 month. Patients were blinded to the target. The study was conducted under an investigational device exemption because the deep brain stimulation system (Kinetra system, Medtronic Inc, Minneapolis, Minnesota) was not approved for use by the US Food and Drug Administration when the study began. Patients underwent bilateral deep brain stimulation lead implantation while awake, during 1 procedure whenever possible; however, some patients returned for the second lead implant due to patient fatigue or technical issues. Lead implantation was accomplished using stereotactic frames with magnetic resonance imaging, computed tomographic guidance, or both. Initial targets were based on standard coordinates for subthalamic nucleus and globus pallidus. Intraoperative microelectrode recording and test stimulation were mandatory to optimize uniformity of implant technique and target localization. Microelectrode recording was expected to demonstrate neuronal activity stereotypical for subthalamic nucleus or globus pallidus targets. Intraoperative test stimulation was performed to assess improvement of parkinsonian signs and occurrence of stimulation-induced adverse effects. All surgeons had significant pre-study expertise with deep brain stimulation surgery and microelectrode recording involving the subthalamic nucleus and globus pallidus and used their clinical judgment to identify the best location for lead implantation. Lead position was revised from the original target at the discretion of the surgeon based on the results of microelectrode recording and test stimulation. The neurostimulator was usually implanted (under general anesthesia) on the same day immediately following lead implantation. Once the stimulator was turned on, patients in the deep brain stimulation group received continuous stimulation. Patients returned as needed for stimulation-parameter adjustments using a standardized protocol to maximize symptom control and minimize adverse effects. Stimulation and medication adjustments were conducted by clinicians unblinded to treatment. Patients who received best medical therapy were managed actively by study movement disorder neurologists after randomization. Neurologists applied state-of-the-art care, including adjuvant medication, and made adjustments to the

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	dosages, frequency, or timing of medication, and to nonpharmacological therapy (eg, physical, occupational, and speech therapy) as needed to achieve best symptom control and optimal functioning.
Results	A total of 255 patients with PD were randomized to receive best medical therapy (n=134) or bilateral deep brain stimulation (n=121; of these patients, 61 were additionally randomized to globus pallidus and 60 to subthalamic nucleus) 19 patients withdrew consent and did not participate (9 DBS 9 BMC); 1 patient died in DBS; 6 people administratively withdrawn when BMC group closed Of 255, 211 completed 3 month evaluation and 224 completed 6 month Characteristics: 82%male, 69% married, mean age = 62.4 (8.9) mean 12.4 (5.8) years since diagnosis, 25% aged 70 or older. No differences in any baseline measure between groups, except: BMC group treated with PD meds for longer (12.6 vs 10.8 yrs) and had lower working memory (97 vs 101) Motor diary • DBS gained a mean of 4.6 hours per day of on time without troubling dyskinesia, while the mean change for the best medical therapy group was 0 hours (95% CI, 3.7-5.4, P<.001). • Off time decreased by 2.4 hours per day and on time with troubling dyskinesia by 2.6 hours per day in patients in the deep brain stimulation group compared with 0 and 0.3 hours per day in patients iBMC group (P<.001). • Asleep time did not change significantly over time by group. • Among those aged 70 years or older, patients receiving DBS gained an average of 3.8 hours of on time per day, whereas patients receiving BMC lost 0.5 hours per day (P<.001). Motor function • Change in off time significantly greater in DBS compared to BMC over 6 months • Motor functioning improved by 12.4 points in DBS vs 1.7 in BMC. In those >70yrs, motor function improved by 9.9 points in DBS vs 1 point in BMC • UPDRS ADL improved significantly in all domains for DBS • When data re-examined using 5 point change in UPDRS as measure of MID, 71% DBS vs 32% BMC improved in motor function at 6 months, 3% DBS and 21% BMC clinical worsening • Walk to sit test: DBS 9s improvement, BMC worsened by 0.2s • Medication decreased by 296mg in DBS and increased by 15mg over baseline for patients in BMC. Quality of Life

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	• Patients who received DBS experienced significant improvements on summary measure and on 7 of 8 PDQ-39 subscales compared with BMC (social support subscale did not change) Neurocognitive function • DBS performed significantly better at baseline on WM tasks • Treatment differences in change between baseline and FU on composite WM, processing speed, phonemic fluency, and delayed recall of brief visuospatial memory test • BMC showed significant improvement 1-2 point increase; DBS group significant decrease 1 - 3.5 points • Neither treatment associated with significant change on Mattis dementia or beck dementia inventory or majority of exec functioning, language, learning and memory The overall incidence risk of experiencing a serious adverse event was 3.8 times higher (95%CI, 2.3-6.3) in deep brain stimulation patients than in best medical therapy patients DBS patients reported 659 moderate/severe adverse events; BMC patients reported 236 moderate/severe adverse events. The most frequent adverse events were falls, gait disturbance, dyskinesia, motor dysfunction, balance disorder, depression, and dystonia (≥9% patients for each). During the 6-month follow-up, there were significantly more events for the deep brain stimulation group than the best medical therapy group for falls (P < .01), gait disturbance (P = .03), depression (P = .03), and dystonia (P<. 01). Surgical site infection (9.9%) and surgical site pain (9.0%) occurred only in the deep brain stimulation group. There was no study site variation in infection rates, ranging from 0 to 2 infections per site. Most differences in adverse events between the 2 groups occurred in the first 3 months; only falls and dystonia were significantly greater for the deep brain stimulation group than for the best medical therapy group in the later 3 months (Table 4). The majority of adverse events (83%) in both groups had resolved by the 6-month follow-up. Forty-nine deep brain stimulation patients (40%) experienced 82 serious adverse events. 68 serious adverse events (83%) were attributed to the surgical procedure, stimulation device, or stimulation therapy. Of the 39 serious adverse events related to the surgical procedure, 26 also were attributed to other concurrent causes. Two deep brain stimulation patients died; 1 death was secondary to cerebral haemorrhage that occurred 24 hours after lead implantation. The second death was due to lung cancer; however, the patient withdrew participation prior to deep brain stimulation implantation. The most common serious adverse event was surgical site infection. Twelve patients had 16 infections related to the surgical procedure or device. These infections resulted in antibiotic therapy and removal of the leads, neurostimulator, or both. By the 6-month follow-up, some patients received implants again. Other serious adverse events included nervous system disorders

Bibliographic reference	**Weaver,Frances M., Follett,Kenneth, Stern,Matthew, Hur,Kwan, Harris,Crystal, Marks,William J.J., Rothlind,Johannes, Sagher,Oren, Reda,Domenic, Moy,Claudia S., Pahwa,Rajesh, Burchiel,Kim, Hogarth,Penelope, Lai,Eugene C., Duda,John E., Holloway,Kathryn, Samii,Ali, Horn,Stacy, Bronstein,Jeff, Stoner,Gatana, Heemskerk,Jill, Huang,Grant D., Study Group, Bilateral deep brain stimulation vs best medical therapy for patients with advanced Parkinson disease: a randomized controlled trial, JAMAJ.Am.Med.Assoc., 301, 63-73, 2009**
	(n=15), psychiatric disorders (n=11), device-related complications (such as lead migration and defective lead wire; n=8), cardiac disorders (n=4), other infections (n = 2), and other events (n=20). Six patients experienced falls resulting in injury. Fifteen best medical therapy patients (11%) experienced 19 serious adverse events. Events included nervous system (n=3), psychiatric (n=2), and cardiac (n=2) disorders; falls (n=2); other infections (n=2); and other events (n=8). Serious adverse events were resolved in 99% of cases by 6 months. Although the serious adverse event rate was higher for deep brain stimulation patients than for best medical therapy patients, there was no difference in the serious adverse event rate between older (26%) and younger (25%) patients. Also, there were no differences in types of serious adverse events experienced by age (results not shown).
Other information	None
Overall Risk of Bias	1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - patient randomized and stratified according to site 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 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: blinded assessment done where possible 14. Investigators were kept blind to other important confounding and prognostic factors: Yes, blinded assessment done where possible

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 • 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.

<table>
<tr><th>Bibliographic reference</th><th>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</th></tr>
<tr><td></td><td>• 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 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>
</table>
</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**
	<table><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)
Other information	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 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

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
	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	Witt,K., Granert,O., Daniels,C., Volkmann,J., Falk,D., van,Eimeren T., Deuschl,G., 20130829, Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial, Brain, 136, 7-19, 2013
Country/ies where the study was carried out	Germany
Study type	NB: THIS STUDY IS A FOLLOW-UP ON NEUROPSYCHOLOGY FROM DEUSCHL ET AL., 2006 (randomized controlled trial)
Aim of the study	To assess the impact of DBS on neuropsychological changes compared to best medical therapy
Study dates	published 2013
Source of funding	Study was supported by the German ministry of research and technology, the German research council, and the internatinal Parkinson Fond Europe K Witt has received lecture fees from medtronic an has been serving as consultant for UCB
Sample size	THIS STUDY IS A FOLLOW-UP ON NEUROPSYCHOLOGY FROM DEUSCHL ET AL., 2006 Subsample of all patients from a single centre (out of 10 centres) in Kiel, Germany n=62
Inclusion criteria	See Deuschl et al., 2006 Subsample of all patients from a single centre (out of 10 centres) in Kiel, Germany
Exclusion criteria	See Deuschl et al., 2006

Bibliographic reference	**Witt,K., Granert,O., Daniels,C., Volkmann,J., Falk,D., van,Eimeren T., Deuschl,G., 20130829, Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial, Brain, 136, 7-19, 2013**
	Subsample of all patients from a single centre (out of 10 centres) in Kiel, Germany
Details	See Deuschl et al., 2006
Interventions	See Deuschl et al., 2006
Results	Demographics (n=62) Mean age = 59.4 (8.6) Disease duration = 13.2 years (5.4) Female = 28 /62 (45%)

Test	DBS_change score	BMC_change score
UPDRS motor	20.0 (11.8)	2.9(9.9)
MDRS	-2.5 (4.9)	-1.1 (4.2)
Backward digit span task	-0.6 (1.6)	0.03 (1.9)
Verbal fluency semantic	-6.1 (11.6)	0.3 (10.3)
Stroop_intereference (Time, sec)	-12.3(51.1)	0.3 (18.3)
Stroop_interference (error rate)	-0.5 (3.6)	-0.3 (2.3)
Verbal fluency letter	-1.9(8.1)	-0.5 (6.0)

Other information	
Overall Risk of Bias	See Deuschl et al., 2006 for risk of bias asssessment

LCIG -v- BMT

Bibliographic reference	**Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014**
Country/ies where the study was carried out	USA (Germany, New Zealand, USA)
Study type	Randomised controlled double-blind double-dummy study
Aim of the study	To assess the efficacy and safety of levodopa-carbidopa intestinal gel delivered continuousy through an intrajejunal percutaneous tube (LCIG)
Study dates	Published Feb 2014, no other dates given
Source of funding	Abbvie (Note: all authors have multiple conflicts of interests with a range of research and pharmaceutical companies)
Sample size	N = 71; n LCIG = 37, n immediate-release oral levodopa-carbidopa = 34
Inclusion criteria	• Adults aged > or = 30 years with advanced PD according to UKBB criteria that was complicated by off-periods that could not be satisfcatorily controlled with optimal medical therapy (excluding apomorphine). • Participants must have received stable doses of levodopa for at least 4 weeks before entollment in the study and had recognizable on-time and off-time with a minimum of 3h of off-time per day based on home assessment • Sustained-release ldopa, stalevo, or other formulations of ldopa wer permitted; doses converted into equivalent doses of immediate-release oral levodopa
Exclusion criteria	Atypical or secondary parkinsonism, previous neurosurgery, psychiatric, or lab abnormalities in the judgement of the investigator, or any condition that may interfere with absorbtion, distribution, metabolism, or excretion of the study drug or contraindicate intrajejunal percutaneous gastrojejunostomy tube
Details	Eligible participants were admitted to hospital for jejunal placement of a percutansous gastrojejunostomy tube under local anaesthesia with endoscopic or fluroscopic guidance, and then randomly allocated (1:1) to tmt with either over-encapsulated immediate-release oral levodopa + placebo LCIG, or LCIG + oral placebo ldopa Randomization done with a central, computer-generated, predetermined, randomization code, and was stratified by site, with a mixed-block size of 2 or 4. An interactive voice response generated the randomization schedule and assigned participantts to tmt group All participants and investigators were masked to group assignment Data analysers were masked until after database was locked Simultaneous titration of active and placebo therapy was done for patients in both groups to maintain the integrity of the masking.

Bibliographic reference	**Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014**
Interventions	Intestinal gel and immediate-release oral forms of Ldopa-cdopa were initially administered at participant's baseline total daily ldopa dose before randomization LCIG delivered as aqueous formulation (20mg/mL ldopa and 5mg/mL carbidopa monohydrate solution) in 100g cassettes or matching placebo gel (sodium carboxymethylase solution alone) administered as morning bolus (5-10 mL) followed by continuous infusion at constant rate for rest of participants waking day (~16hr). Infusion stopped overnight Immediate release ldopa capsules containing 25mg carbidopa and 100mg levodopa or matching placebo initially initiated in divded doses overwaking day beginning at same time as infusion and at same dose frequeny as baseline. 4 titration during which dosing for patients in either group could be adjusted by changing the infusion rate in 100mg daily increments; ldop/cdopa immediate-release could be adjusted by changing infusion rate in 100mg daily increments Changes in dose made soley on basis of investigator judgement; participants could not change dose or schedule any change in dose of active intervention in a participant had to be matched by corresponding change in placebo (to maintain masking) Dose adjustment could be made in either LCIG or oral Ldopa/cdopa treatments so that all patients were titrated to their optimum state Titration period was followed by 8 week maintenence period during which patients were maintained on stable doses of their asisigned treatment Open-label immediate-release oral ldopa/cdopa could be used as rescue therapy for persistent off-episodes for patients in either group Study visits conducted as baseline and weeks 1, 2, 3, 4, 6, 8, 10, and 12 For 3 consecutiv days before each visit begginning at week 2, pts completed a 24hr diary asssessment of motor status at 30min intervals, recording if they were in an off-state in an on-state without dyskinesia, in an on-state with non-troublesome dyskinesia, in a on-state with troublesome dyskinesia, or asleep Before assesment, pts trained in use of diary and had to have >75% concordance with investigator and .75% compliance with completing diary Additional assessments at each visit included assessment of vital signs, UPDRS in on and off states, PDQ-39, EQ5D, zarit carer burden interview, and investigator-rated CGIC Safety assessments done at each visit In 1st 20 participants, plasma concentrations of levodopa measures at multiple time points after initiation of LCIG For remaining pts, sampling done at 6 weeks before start of infusion and 1, 2, 4, 8hr after infusion

Bibliographic reference	**Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014**
	Statistical analyses • Analysed primary end point with ANCOVA model, including effects for treatment group and country, with baseline off time and average daily rescue levodopa
Results	Demographics: • Gender: 65% male in both groups • Disease duration: 10 (4.6) LCIG, 11.8 (5.6) Ldopa • UPDRS (overall): 31.5 (18.0) LCIG, 35.8 (18.9) ldopa • MMSE = 28.8 (1.4) both groups Completion: 35 in LCIG: 2 drop out: 1 halllucination and psychosis, 1 protocol disorder; 31 in ldopa: 3 drop-out; 1 peritonitis, 1 stoma dysfunction, 1 lack of efficacy 71 patients enrolled at 26 centres - mean 2.6 patients per centre Titration to stable dose achieved at mean 7 days (2.5) for participants in LCIG and 8 days (2.5) in immediate-release oral levodopa carbidopa group - 88% subjects titrated to stable dose in < or = 9 days Efficacy analysis Significant improvements in LCIG for off-time on time without duskinesia, PDQ-39, CGIC, UPDRS II. For off time per day LCIG > reduction in off-time between baseline and wk 12 than immediate-release ldopa, also ass with > improvement in on-time without troublesome dyskinesia, and on-time without dskinesia.

Outcome	LCIG	Ldopa	MD 95%CI
Off-time h/d	-4.04(0.65)	-2.14 (0.66)	-1.91(-3.05 to -0.76)
On time w/o trouble dysk	4.11 (0.75)	2.24 (0.76)	1.86 (0.56 to 3.17)
On time w/o dysk	3.37 (1.04)	1.09(1.05)	2.28 (0.47 to 4.09)
On-time with dysk	0.81 (0.86)	1.54 (0.86)	-0.73 (-2.22 to 0.76)
PDQ-39 (summ index)	-10.9 (3.3)	-3.9 (3.2)	-7.0 (-12.6 to - 1.4)

Bibliographic reference	**Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014**

CGIC	2.3 (0.4)	3.0 (0.4)	-0.7 (-1.4 to -0.1)
UPDRS II	-1.8 (1.3)	1.3 (1.3)	-3.0 (-5.3 to -0.8)
UPDRS III	-1.5 (2.4)	-2.9 (2.4)	1.4 (-2.8 to 5.6)
EQ5D	0.05 (0.04)	-0.02 (0.04)	0.07 (-0.01 to 0.15)
Carer burden	-2.8 (3.7)	1.7 (3.3)	-4.5 (-10.7 to 1.7)
Levodopa total daily dose	91.7 (96.6)	249.7 (94.9)	-158.0 (-324 to 8.5)
Overall mean ldopa rescue dose	139.8 (20.3)	180.6 (21.9)	-40.8 (-100.4 to 18.8)

Other information

Adverse events	LCIG (n=37)	ldopa (n=34)	overall (n=71)
Any adverse event	35 (97%)	34 (100%)	69
Serious adverse event	5 (14%)	7 (21%)	12
Abdominal pain	19 (51%)	11 (32%)	30
Wound infection	4 (11%)	8 (24%)	12
Device complications	34 (92%)	29 (85%)	63

Most adverse events were related to the surgucal procedure or device, mild to moderate in severity, occurred almost exclusively within the first week, and resolved in all cases.

Overall Risk of Bias

1. An appropriate method of randomization was used to allocate pts to treatment groups: Yes - patient randomized externally
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: Yes - all participants blind to condition
6. Individuals administering care were kept blind to tmt allocation: Yes

Bibliographic reference	Olanow,C.W., Kieburtz,K., Odin,P., Espay,A.J., Standaert,D.G., Fernandez,H.H., Vanagunas,A., Othman,A.A., Widnell,K.L., Robieson,W.Z., Pritchett,Y., Chatamra,K., Benesh,J., Lenz,R.A., Antonini,A., Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomised, controlled, double-blind, double-dummy study, The Lancet Neurology.13 (2) (pp 141-149), 2014.Date of Publication: February 2014., 141-149, 2014
	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 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: Yes 14. Investigators were kept blind to other important confounding and prognostic factors: Yes