Best Medical Therapy vs. Deep Brain Stimulation for Parkinson's Disease:

Six Month Results from a Multi-Site Randomized Trial

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Parkinson's disease (PD)

- Diagnosed based on symptoms
  - Tremor
  - Bradykinesia
  - Rigidity
  - Postural instability (gait & balance)
- Gold standard treatment is medication - levodopa

Considerations for Surgery in PD

- Levodopa becomes less effective
  - Good response in the past
  - Longer periods in off state
  - Dyskinesia
  - Motor fluctuations – on/off, end of dose wearing off
- Psychological status good
- Otherwise good candidate for surgery

Background

- Deep Brain Stimulation (DBS) is an accepted surgical intervention for PD patients who have motor complications with medication. However, several questions remain, such as
  - When should DBS be offered? (stage of illness)
  - Who are the best candidates for DBS?
  - In what site of the brain is DBS for PD most effective? (phase II)
  - How does DBS compare to best medical therapy (BMT)? (phase I)

Previous Work

- Deuschl et al. (NEJM, 2006), using a matched pairs design, found that while DBS patients improved significantly on motor function, about one-third did not improve over their matched, medically treated controls on motor function.
- We present 6-month results of a large randomized control study comparing DBS to BMT that included a significant number of older patients.

Primary Objectives- Phase I

- To compare patient motor function, based on self-report motor diaries at six months following DBS or BMT in patients with PD.
- To compare objective motor function, using the Unified Parkinson's Disease Rating Scale (UPDRS) for PD patients who undergo bilateral DBS or receive BMT at six months.

Phase II

- DBS patients randomized to site of surgery
  - Subthalamic nucleus (STN)
  - Globus pallidus interna (GPi)
- BMT continued on to surgery after six months (STN v. GPi)
- Primary objective: to compare motor function (UPDRS part III) at 2 years for STN v. GPi DBS patients (subgroup with 3 yrs of data)

Patient Eligibility Criteria

- Hoehn & Yahr stage ≥ 2 when off medications
- Idiopathic PD, responsive to levodopa
- Off time or on time with troubling dyskinesia ≥ 3 hours/day
- No contraindications to surgery; no prior PD surgery
- No cognitive impairment or dementia
- On stable dose of PD medications for at least one month

Methods

- Patients were stratified by study site and by age (<70 vs. ≥70 years) and randomized to BMT or DBS.
- DBS patients were then randomized to surgical target: bilateral subthalamic nucleus (STN) or globus pallidus interna (GPi).
- Phase II (not yet reported) – BMT patients continued on with randomization to GPi or STN and were followed for two to three years, along with original DBS arm.

Methods

- Six month data included:
  - Patient self-report motor diaries.
  - Motor function using the UPDRS (part III)
    - Unblinded & blinded assessments.
  - Quality of Life using the Parkinson's Disease Questionnaire-39 (PDQ-39).
  - Other UPDRS subscales, adverse events, levodopa equivalents, neuropsychological outcomes.

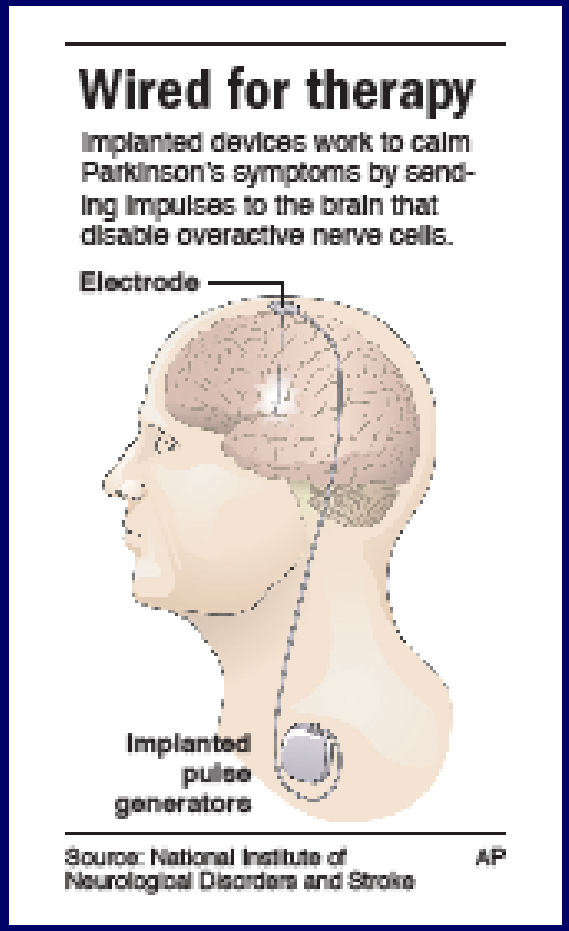
Blinded Assessments

- A neurologist, not part of the study, conducted independent evaluations of patient motor function using the UPDRS (part III)
- Patients wore caps and gowns to cover any possible surgical scars

Best Medical Therapy

- Actively managed by movement disorder specialists
- PD medications with adjustments in dose, frequency and timing as needed
- Use of therapies (physical, occupational, speech) as needed
- Goal was to achieve best symptom control and optimize function

Diagram of DBS Procedure



DBS Procedure

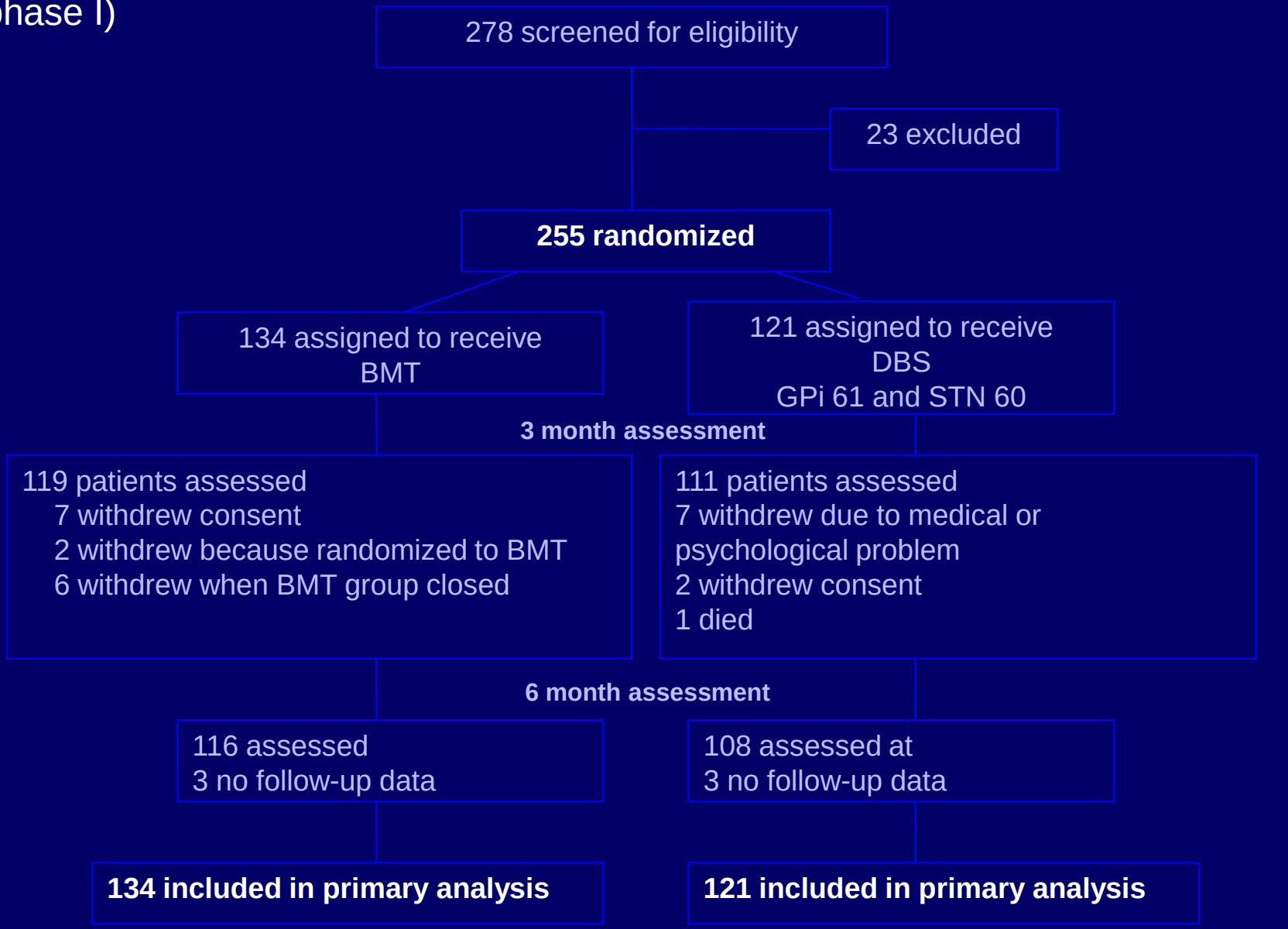
- Lead implantation using stereotactic frames and MRI and/or CT guidance
- Intraoperative microelectrode recording and test stimulation used to optimize target location
- Bilateral implantation on same day whenever possible
- Implant of pulse generator (Kinetra) under general anesthesia, usually on the same day
- Stimulator turned on within one week in majority of cases
- Patients provided with hand-held controllers for minor stimulator adjustments

Participating Sites

- VA (PADRECCs)
  - Richmond
  - Philadelphia
  - West Los Angeles
  - San Francisco
  - Houston
  - Portland/Seattle
- University sites
  - Medical College of Virginia
  - University of Pennsylvania
  - UCLA
  - UCSF
  - Baylor
  - Oregon Health Science University

Patient Enrollment and Randomization Assignment

(phase I)



Patient Baseline Characteristics by Treatment Group

	BMT (n=134) Mean (std) or %	DBS (n=121) Mean (std) or %	p-value
Age (yrs)	62.3 (9.0)	62.4 (8.8)	0.974
Age 70 or greater	27.6%	25.6%	0.777
Male	82.1%	81.0%	0.872
VA patient	59.7%	60.3%	1.000
Years on PD medications	12.6 (5.6)	10.8 (5.4)	0.013
White	95.5%	96.7%	0.752
Married	70.9%	66.9%	0.502
Living with family	76.1%	82.6%	0.365
Has personal caregiver help	44.8%	46.3%	0.900
Family history of PD	23.9%	26.4%	0.666
Hoehn-Yahr (H-Y) off med	**3.3(0.8)**	**3.4(0.9)**	**0.848**
Schwab-England (S-E) off med	51.0(19.7)	50.4(20.5)	0.802

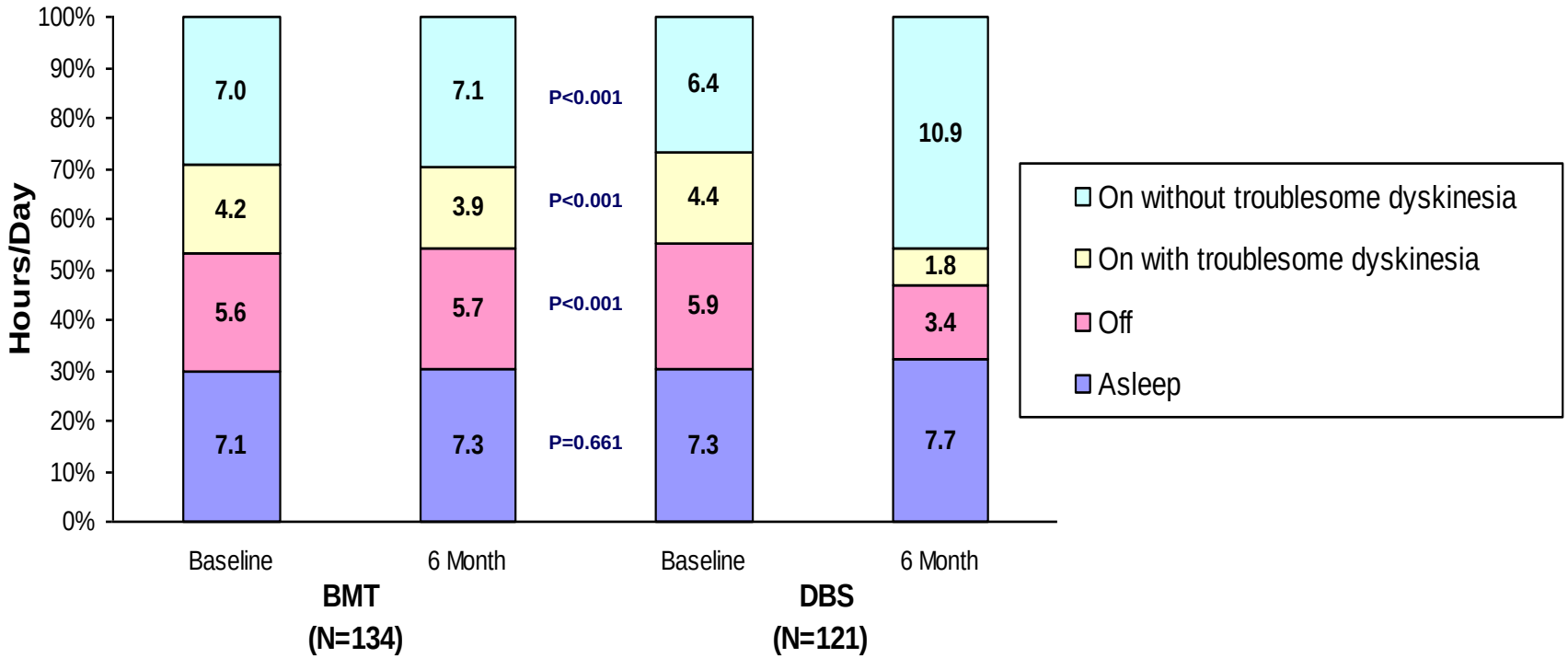
Patient Baseline Characteristics by Treatment Group

	BMT (n=134) Mean (std) or %	DBS (n=121) Mean (std) or %	p-value
Motor function (blinded/off med)	43.2(11.3)	43.0(13.5)	0.878
Mentation/behavior/mood (UPDRS I)	2.7(2.0)	2.6(2.0)	0.687
Activities of daily living (UPDRS II)	19.7(6.1)	19.1(5.9)	0.438
Complication of therapy (UPDRS IV)	9.3(3.1)	9.2(3.0)	0.788
On w/o troublesome dyskinesia (hrs)	7.0(2.9)	6.4(2.7)	0.068
On w/ troublesome dyskinesia (hrs)	4.2(3.1)	4.4(3.1)	0.589
Mobility (PDQ-39)	58.4(21.4)	61.1(21.0)	0.297
ADL (PDQ-39)	54.8(18.8)	55.0(17.6)	0.917
Emotional well being (PDQ-39)	39.7(18.6)	38.4(19.3)	0.568
Social support (PDQ-39)	26.0(18.0)	26.9(19.6)	0.713

Patient Baseline Characteristics by Treatment Group

	BMT (n=134) Mean (std) or %	DBS (n=121) Mean (std) or %	p-value
Beck depression inventory	11.7(8.1)	11.3(8.7)	0.680
Mattis Dementia rating scale	136.6(5.8)	136.7(4.8)	0.842
Processing speed index	89.4(14.1)	91.0(13.9)	0.366
WAIS-III Working memory index	97.3(13.6)	101.2(13.3)	0.023
Phonemic Fluency (FAS)	44.7(12.1)	45.7(12.1)	0.520
Category Fluency (Animal)	49.5(11.6)	50.9(11.3)	0.336
HVLT total (learning/memory)	39.9(11.5)	38.9(11.3)	0.499
HVLT delayed recall	38.1(13.4)	37.3(13.3)	0.619
Finger tapping	37.6(12.9)	37.1(11.4)	0.746
Boston Naming Test (language)	55.9(4.3)	55.5(4.5)	0.444

Patient Motor Diary Outcomes



Younger DBS patients – on time improved by an average of 5.2 hours/day
Older DBS patients – on time improved by an average of 3.8 hours/day

Motor Function Outcomes at Baseline and Six Months by Treatment Group

	BMT (n =134)		DBS (n = 121)		BMT - DBS	
Outcome	Baseline	6 Months	Baseline	6 Months	Diff (95% CIs)	P-value
Hoehn and Yahr – off meds	3.3 (0.8)	3.4 (0.9)	3.4 (0.9)	2.8 (0.9)	0.5 (0.3, 0.7)	<0.001
Schwab and England – off meds	51.0 (19.7)	49.3 (19.5)	50.4 (20.5)	66.2 (22.1)	-17.5 (-22.2, -12.8)	<0.001
Stand-walk-sit – off meds (seconds)	36.3 (37.9)	36.9 (62.2)	34.6 (36.7)	25.2 (24.1)	8.8 (0.1, 17.5)	0.046
UPDRS I –Mentation/ Behavior/Mood	2.7 (2.0)	3.0 (2.1)	2.6 (2.0)	2.6 (2.3)	0.3 (-0.2, 0.8)	0.299
UPDRS II – ADL	**19.7 (6.1)**	**19.7 (5.9)**	**19.1 (5.9)**	**14.5 (6.9)**	**4.6 (3.4, 5.9)**	**<0.001**
UPDRS III -Motor blind/on med/on stim	23.4 (11.1)	23.1 (11.7)	22.6 (12.6)	20.3 (11.3)	2.0 (-0.2, 4.2)	0.075
UPDRS III -Motor blind/off med/on stim	**43.2 (11.3)**	**41.6 (12.7)**	**43.0 (13.5)**	**30.7 (14.5)**	**10.6 (8.1, 13.2)**	**<0.001**
UPDRS IV – complications	9.3 (3.1)	8.8 (3.2)	9.2 (3.0)	5.8 (3.0)	2.9 (2.1, 3.7)	<0.001
Levodopa equivalents (mg)	1289 (546)	1303 (532)	1281 (521)	985 (633)	310 (182, 439)	<0.001

Quality of Life at Baseline and Six Months by Treatment Group

	BMT (n =134)		DBS (n = 121)		BMT - DBS	
Outcome	Baseline	6 Months	Baseline	6 Months	Diff (95% CIs)	P-value
PDQ-39 Mobility	58.4 (21.4)	58.0 (22.2)	61.1 (21.0)	48.8 (25.2)	12.0 (7.9, 16.1)	<0.001
PDQ-39 ADLs	54.8 (18.8)	56.3 (19.1)	55.0 (17.6)	41.0 (22.2)	15.5 (11.9, 19.2)	<0.001
PDQ-39 Emotional well-being	39.7 (18.6)	38.4 (18.5)	38.4 (19.3)	32.6 (19.5)	4.4 (0.7, 8.2)	0.020
PDQ-39 Stigma	44.0 (24.5)	39.8 (25.5)	40.6 (24.3)	28.2 (23.7)	8.3 (3.6, 13.1)	0.001
PDQ-39 Social Support	26.0 (18.0)	27.5 (19.0)	26.9 (19.6)	25.1 (21.1)	3.2 (-1.4, 7.8)	0.170
PDQ-39 Cognition	42.2 (17.9)	43.8 (16.6)	40.4 (17.8)	36.7 (20.4)	5.3 (1.3, 9.4)	0.011
PDQ-39 Communication	45.2 (17.9)	47.8 (18.5)	45.3 (20.0)	42.6 (22.6)	5.2 (1.2, 9.3)	0.013
PDQ-39 Bodily Discomfort	47.6 (21.6)	48.6 (24.3)	51.2 (21.2)	44.0 (21.1)	8.3 (3.8, 12.7)	<0.001
PDQ-39 Single Index	44.3 (13.1)	44.8 (13.4)	44.9 (13.2)	37.3 (16.0)	8.1 (5.6, 10.5)	<0.001

Neuropsychological Outcomes at Baseline and Six Months by Treatment Group

	BMT (n =134)		DBS (n = 121)		BMT - DBS	
Outcome	Baseline	6 Months	Baseline	6 Months	Diff (95% CIs)	P-value
Mattis Dementia Total Score	136.6 (5.8)	137.5 (5.5)	136.7 (4.8)	136.6 (6.7)	1.1 (-0.3, 2.4)	0.122
WAIS-III Working memory index	97.3 (13.6)	98.3 (14.9)	101.2 (13.3)	99.6 (13.6)	2.6 (0.8, 4.4)	0.005
WAIS-III Processing speed index	89.4 (14.1)	90.1 (13.9)	91.0 (13.9)	88.4 (14.3)	2.9 (0.8, 4.9)	0.006
Category Fluency (Animal)	49.5 (11.6)	47.4 (11.9)	50.9 (11.3)	46.2 (11.3)	2.6 (-0.2, 5.4)	0.064
Phonemic Fluency (FAS)	44.7 (12.1)	45.7 (11.8)	45.7 (12.1)	42.2 (12.3)	4.6 (2.5, 6.6)	<0.001

Neuropsychological Outcomes at Baseline and Six Months by Treatment Group (cont.)

	BMT (n =134)		DBS (n = 121)		BMT - DBS	
Outcome	Baseline	6 Months	Baseline	6 Months	Diff (95% CIs)	P-value
Boston Naming Test	55.9 (4.3)	56.2 (4.0)	55.5 (4.5)	56.2 (3.8)	-0.4 (-0.8, 0.1)	0.127
Finger Tapping	37.6 (12.9)	38.7 (13.2)	37.1 (11.4)	36.9 (11.3)	1.3 (-1.2, 3.8)	0.319
Stroop Interference	51.0 (7.6)	51.8 (8.4)	50.7 (7.4)	49.8 (7.1)	1.6 (-0.4, 3.5)	0.111
BVMT Delayed Recall	42.4 (13.3)	44.6 (13.7)	42.1 (13.3)	41.1 (13.6)	3.2 (0.4, 6.0)	0.026
Beck Depression Inventory	11.7 (8.1)	10.2 (6.9)	11.3 (8.7)	10.9 (8.6)	-1.0 (-2.7, 0.6)	0.224

Total Adverse Events by Treatment Group

	BMT (N=134)	DBS (N=121)
Adverse Events (AE)		
Mild	293	799
Moderate	206	555
Severe	30	104
Total*	530	1464
Serious Adverse Events (SAE)**	19	82

* 1 BMT and 6 DBS cases missing level of severity.

** An SAE is defined as any event that: results in death, is life-threatening, results in prolonged or new hospitalization, results in disability or congenital anomaly/birth defect, or requires medical or surgical intervention to prevent one of the above outcomes.

Most Frequent Moderate and Severe Adverse Events

Adverse Events	AEs from randomization to 3 months (# events)			AEs from four to six months (# events)		
	BMT	DBS	P-value	BMT	DBS	p-value
Fall	**6**	**17**	**0.015**	**5**	**14**	**0.029**
Gait disturbance	9	16	0.137	4	10	0.097
Dyskinesia	11	9	1.000	5	12	0.076
Motor dysfunction	9	13	0.272	6	3	0.505
Balance disorder	6	13	0.140	4	6	0.525
Pain	3	13	0.043	3	9	0.123
Speech disorder	2	13	0.004	3	7	0.199
Dystonia	5	11	0.182	1	8	0.015
Headache	1	22	<0.001	0	1	0.475
Bradykinesia	4	13	0.036	3	4	0.711
Confusional state	1	15	<0.001	3	3	1.000
Freezing phenomena	6	5	1.000	3	7	0.199

Serious Adverse Events

- 49 DBS patients experienced a total of 82 SAEs, while 15 BMT patients experienced 19 SAEs.
- The overall incidence risk ratio (IRR)* of experiencing an SAE was 3.8 times higher (95% CI: 2.1-6.7) in DBS than BMT patients.

*IRR calculated as the number of new SAEs divided by the total person-time of follow-up.

Serious Adverse Events by Treatment Group

	BMT (N=19)	DBS (N=82)
Device/Procedure Related		
Implant site infection	N/A	16*
Complication/migration/discomfort	N/A	6
Subdural hematoma	N/A	1**
Nervous System		
Dyskinesia	0	2
Akinesia	1	0
Balance disorder	0	1
Motor dysfunction	0	1
Other	2	11***
Psychiatric		
Mental status changes	0	3
Confusional state	0	2
Hallucination	1	1
Depression	0	1
Other	1	4
Neoplasms	0	4
Other diseases/conditions (e.g., cardiac, GI, other infection)	12	23

* Twelve patients experienced 16 infections. All ultimately had electrodes, pulse generator, or both explanted.
** Patient had subdural hematoma. Device explanted. Died several days later.
*** Includes 2 CVAs.

Conclusions

- DBS was superior to BMT in improving motor function and quality of life in a large cohort of PD patients.
- The on time gain (4.6 hours) is significantly larger than gains seen with adjunctive medications reported in other published studies (average +1-2 hours of on time).
- Quality of life improved significantly for DBS with little change in the BMT group.

Conclusions cont.

- There were a large number of SAEs experienced by DBS; 10% infection rate. However, these were resolved within 6 months. A large number of AEs in general were related to disease progression and other chronic conditions.
- Older patients did almost as well as younger patients following DBS on motor function and quality of life.
- Physicians and patients should weigh the potential short and long term risks vs. benefits of DBS in making decisions about surgical interventions for PD.

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