

## The Cost Benefit and Effectiveness Anlayze of DBS Therapy on Parkinson's Disease in Four Different University Hospitals in Turkey

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### Abstract

Parkinson disease (PD) represents 75% of all parkinsonian syndromes and is a chronic, slow progressive neurodegenerative disorder. In 2030, the population of PD patients all over the world is expected to reach to 8.7-9.3 million of patients. In 1997, Deep Brain Stimulation (DBS) was firstly approved as an alternative treatment option in PD patients. In Turkey although DBS was reimbursed for the treatment of PD since 2009, we could not reach out any cost analyze studies. Our primary aim with four different university hospitals 60 patients' data is to compare the costs of one year best medical treatment and DBS in the first year after its application. Second approach was to evaluate the pre and post-operative conditions via UPDRSIII and Hoehn and Yahr rating scales. Total one-year implantation cost was calculated 58.079,82 TL per case. The cost benefit outcomes were changes in UPDRS III and Hoehn and Yahr after DBS treatment were 7.1 and 1.13 points, respectively. All values have been verified with wilcoxon, friedman and one sample Kolmogorov statistical analyzes. In terms of cost effectiveness and minimization, the result could not be achieved in comparing one-year cost datas. Long term studies involving more centers and patients should be undertaken in future.

**Keywords:** Parkinson disease; Deep brain stimulation; Cost benefit

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### Introduction

#### Parkinson's disease and economical impacts

In 1817 Parkinson's disease was first described as a neurological syndrome by James Parkinson [1]. Parkinson's Disease (PD) is the most common neurodegenerative disease after Alzheimer's disease [2]. PD prevalence is increasing with age and PD affects 1% of the population above 60 years [3]. 5% of PD patients the disease begins under age 40 [4]. In young onset patients, PD is likely developed because of the genetic mutations [5]. It has been also reported in another study that PD population increases after the age 80 with 4% [6]. This increase will bring social and economic burden directly and indirectly. In a recent study conducted in the United States, PD patients' annual health expenditure per case have been reached to 22K US\$ level [7]. The impact of PD to the health care system in UK with direct and indirect cost evaluation has been found out to be between 449 million-3.3 billion pounds [8]. Furthermore, a recent study from Japan reported the annual direct cost as 37,9 K US\$ and indirect costs as 25,3K US\$ [9].

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## Treatment options in Parkinson's disease and deep brain stimulation therapy

Levodopa is the gold standard agent in treatment of PD [10]. Besides Levodopa, medical treatment of PD includes several other pharmaceutical agents such as dopamine receptor agonists, monoamine oxidase B inhibitors (MOA B inhibitors), catechol O methyl transferase inhibitors and amandatin [11]. Mesenchymal Stem Cells applications are investigated to create a different treatment method for PD by molecular biologists, tissue and bioengineers [12]. Especially patients with PD in advanced stage may require device supported therapies such as Apomorphine (Apomorphine pump), Levedopa-Carbidopa Intestinal Gel Infusion Therapy and Deep Brain Stimulation (DBS) [13].

AL Benabid, French neurosurgeon from Grenoble, first introduced the deep brain stimulation (DBS) technique for the treatment of parkinsonian tremor [14]. DBS has been used successfully to treat various diseases of neurological and psychiatric disorders including Parkinson's disease, neuropathic pain and dystonia and has shown great promise in treating addiction, Tourette syndrome, obsessive compulsive disorder [15]. In addition, there are also some beneficial clinic outcomes for the resistant hypertension [16]. There are also some undergoing clinical trials with DBS technology in various critical diseases such as; Alzheimer, Schizophrenia and Stroke [17-19].

DBS system contains tree main implantable and biocompatible materials; a) active implantable pulse generator (IPG) – it is subcutaneously implanted on right or left clavícula bone, b) second part is extensions which are introduced under tissue from scalp base region to clavícula area by tunneling, c) the one of the most important part is the Lead, it is implanted to the deep brain nuclei [20].

In 1997, FDA approved DBS for the treatment of Essential Tremor and other Tremor diseases. Later in 2002 it has also been approved for advanced Parkinson Disease by FDA. In 2016, DBS has been approved for Earlier Stages of Parkinson Disease by FDA [21]. There are 3 main manufacturers in global market for DBS products: (alphabetically); Abbot (Illinois-USA), Boston Scientific (California, USA) and Medtronic (Minnesota, USA) [22]. According to outcome from 143 different centers' survey for DBS surgery steps: the result is mostly applied with 3 main sessions. First part is pre-operative scans with MRI and CT, fusion the images from planning software and obtaining DBS lead target on brain nucleus area. Second part is intraoperative tests (with microelectrode recording or direct targeting), surgical lead implantation (under general or local anesthesia). Final part is verification of DBS Lead implantation by CT (Computer Tomography) scans, MRI (Magnetic Resonance Imaging) or any other intra operative technique and later implanting the IPG [23].

### DBS therapy clinical evaluation

Although DBS treatment has started to be used since 1997; there are still ongoing studies about this therapy. DBS is surgically applied by neurosurgeons however in terms of diagnosing the proper indication for the surgery; intra operative tests, neurological follow up after the surgery, it is also definitely

managed by Neurologists. In terms of psychiatric disorders and patients' psychiatric evaluation, psychiatrists are also involving to this multi-disciplinary study group [24]. The ideal multi-disciplinary DBS center should contain neurology, neurosurgery, neuropsychiatry and neurophysiology specialties [25,26]. DBS battery on stage changes according to different center from 5 day to 30 days during the follow up period [27-29]. In order to improve the clinical effectiveness and benefits, it is recommended that frequent follow up procedure after DBS surgery should be done with the cycle 3, 6-12 months period [30]. In terms of rating scales for PD before and after DBS clinical follow up, UPDRS(UnifiedParkinsonDiseaseRatingScale)III and H&Y(Hoehn Yahr) scales are used a kind of the actual literature [31]. In terms of the verification of DBS patients data's; there are some statistical analyses and methods are preferred such as; Wilcoxon One Sample Pairing Test, Markov and Monte Carlo Simulations [32,33].

### DBS cost evaluation and our study aim

The annual cost (direct and indirect) related to Parkinson's Disease (PD) has been evaluated with 645.000 patients in a research in USA and the total outcome was 23 billion US dollars impact to annual health care budget in 2005 [34]. In same country in 2019, there is a published another study which presents annual cost (direct and indirect) per case from PD is 23 thousand US dollars [35]. In another literature for the cost evaluation research about the assessment of PD with 5 years data from business efficacy, life quality and cost effectiveness values present annual direct cost 37,9 K US dollars and indirect cost 25,3K US dollars impact per case to the Japanese health care system [36]. This kind of outcomes initiate the demands for the cost and quality analyses in PD and related new treatment options like DBS Therapy [37,38].

The DBS Therapy annual cost impact to the US health care system per case is around 35K-100K US dollars [39] and for other health care systems like in Japan is around 29,7K US dollars per case [40], in Germany is around 30K euro per case [41] and in Canada is around 21-24 K Canadian dollars per case [42].

In Turkey, since 2014 DBS is reimbursed by Turkish Republic Social Security Institution only for the tertiary health institution hospitals and for patients with PD, Dystonia and Essential Tremor. The primary aim of our study is to analyze and compare the costs between the best medical treatment and DBS in the first year after the surgery. Our secondary aim was to further analyze clinical outcomes after surgery. For this purpose 4 different university hospitals and 60 patients were included.

## Material and Methods

### Aim of the study

The type of the study is retrospective data analyses. The Ethical Committee submission has been done and the approval has been received on 22nd May 2019.

The study has been performed between June 2017-May 2019 time frame with two different state university hospital and two foundation university hospital. Total number of centers is four.

All Deep Brain Stimulator (DBS) system suppliers in Turkey are US manufacturers such as (alphabetically); Abbot (Austin, Texas),

Boston Scientific Neuromodulation (Valencia, California) and Medtronic (Minneapolis, Minnesota). All these three companies' DBS products have reimbursement according to Turkish Social Security System. There is no disclosure with this study with any of above written companies' name. There is no conflict of interest.

The aim of the study is to evaluate the cost and clinical outcomes of DBS therapy and best medical therapy in sixty DBS implanted patients with comparison one year before DBS surgery and six months – one year after DBS surgery.

### Universe, sample and the time interval

Deep Brain Stimulation (DBS) therapy is currently applied around 35 different centers in government university hospital, government research and educational hospital, foundation university hospital and private hospital status in Turkey. Two government university hospitals and two foundation university hospitals which have approved, were included in study and the details about the centers are below in **Table 1**.

The time interval of the study between June 2017 – May 2019 with sixty patients which have been selected for DBS therapy and evaluated one year before and after six months – one year from the surgery.

### Data sources

All sixty patients who have undergone DBS surgery have been included by four different university hospitals according to the patient selection criteria by Turkish Social Security Directives.

Centers and patient numbers are respectively 26 patient data from Bahçeşehir University Hospital, 15 patient data from Erzurum Atatürk University Hospital, 15 patient data from Hatay Mustafa Kemal University Hospital and 4 patient data from Koç University Hospitals.

### Patient inclusion criteria

All sixty patients were included and selected to this study from each clinics Psychiatry, Neurology and Neurosurgery departments approvals according to Turkish Social Security Directives which have been issued on 1<sup>st</sup> October 2014. In this directive, all sixty PD patients have been diagnosed with bradykinesia and dyskinetic movement from each centers' Neurology clinics although all medical treatments have been applied to each patient. And it must be written in each patient's committee report like that all medical and any other treatment methods have been trialed for each patient and to get better outcome DBS surgery is necessary. All committee reports must be approved by psychiatrist,

neurologist and neurosurgeons as three multi-disciplinary physician group and finally approved by each center's medical director. For reimbursement of the DBS therapy, the status of each hospital should be at 3<sup>rd</sup> step which could be government university or research and educational clinic and foundation university hospitals.

### Cost data

The following cost criterias have been used for comparing the increased cost effectiveness rate from each patient's files:

### Before the DBS Surgery

#### The cost of the best medical treatment

The drug doses used by patients were determined as the equivalent dose of levodopa

#### Outpatient clinic cost including:

- The cost which have been invoiced to Social Security Institute by Government university hospitals, were included.
- In addition to the cost related by foundation university hospitals to the Social Security Institute, copayments which have been collected from each patient according to the limitation with the legal rules.

#### Hospital and Physician visit cost including:

- The transportation and related costs were included to the total cost which were collected by each patient' with aid of physician side data sharing.

### After the DBS Surgery

#### DBS surgery cost:

- For government university hospitals, the cost according to Social Security Institute Directive have been included and for foundation university hospitals, copayments which have been collected from each patient according to the limitation with the legal rules have been included.

#### DBS device cost:

- All DBS devices for each 60 patients was rechargeable technology and the cost was fixed according to Turkish Social Security Institute Directive. The device from any company was not specifically selected and was not referenced.

**Table 1:** Physician and Clinical Detail Information of the Study Centers.

Center No	Study Center Name	Study Center Status	Participant Physicians' Names and Titles	Participants' Specialities	Experience in DBS
1	Bahçeşehir University Medicalpark Hospital	Foundation University Hospital	Akın Akakın - Associate Professor	Neurosurgeon	8 years
2	Koç University Hospital	Foundation University Hospital	Özgür Öztıp Çakmak - Medical Doctor	Neurologist	2,5 years
3	Erzurum Atatürk University Hospital	Government University Hospital	Mürteza Çakır - Associate Professor Mustafa Ceylan - Associate Professor	Neurosurgeon Neurologist	2 years
4	Hatay Mustafa Kemal University Hospital	Government University Hospital	Atilla Yılmaz - Associate Professor	Neurosurgeon	3,5 years

### The cost of the best medical treatment used:

- The drug doses used by patients were determined as the equivalent dose of levodopa

### Outpatient clinic cost:

- The cost which have been invoiced to Social Security Institute by Government university hospitals, were included.
- In addition to the cost related by foundation university hospitals to the Social Security Institute, copayments which have been collected from each patient according to the limitation with the legal rules.

### Hospital and Physician visit cost:

- The transportation and related costs were included to the total cost which were collected by each patient' with aid of physician side data sharing.

### Clinical outcome data

All the clinical data for each 60 participated patients to the study were evaluated by their same Neurologists and Neurosurgeons. In the study, first one year follow up data of the patients were obtained before the DBS surgery. The study was designed as Retrospective Cost Analysis. The scope of the study was the study consisted only of Parkinson's Patients and clinical outcomes and costs associated with pharmaceutical therapy before and after DBS surgery were taken as a method of the treatment. UPDRSIII (Unified Parkinson Disease Rating Scale III) and Hoehn and Yahr scales were used before and after the DBS therapy. The clinical outcomes and disease progress have been measured and scored.

## Results

The results of the study have been evaluated in three main approaches such as clinical outcome, cost outcome and cost effectiveness analysis.

### Clinical outcome analysis

The clinical data from sixty patients have been analyzed with 4 different clinical outcomes such as Drug Dosage Changes Analysis, The changes of UPDRSIII outcome, The changes of Hoehn and Yahr outcome and outpatient visit numbers outcomes.

### Drug dosage changes analysis

Mean Levodopa Equivalent doses were taken from each of the four clinics for sixty patients in 3 different time frames below.

In the first six months after the DBS surgery, a decrease in the daily dosage of Levodopa equivalent was found in a mean of 53,82% in 60 patients. This rate has increased to a mean of 57,50 % in the first year after DBS surgery (Table 2).

### The changes of UPDRSIII outcome

UPDRSIII Outcomes from sixty patients and four different centers have been obtained in 3 different time frames below.

The Table 2 has been created according to the UPDRSIII outcome changes of 60 patients below.

The significant decrease in UPDRSIII and Hoehn & Yahr scores in the first year after DBS is shown in Table 2.

### The changes of Hoehn and Yahr outcome

Hoehn and Yahr Outcomes from sixty patients and four different centers have been obtained in 3 different time frames below.

The preliminary comparison outcomes between before DBS and after six months from DBS was decreased the mean Hoehn & Yahr from 2,98 to 1,58 for sixt patients. The mean Hoehn & Yahr outcome decrease after one-year DBS was to 1,27 for sixt patients (Table 3).

### Outcome from the outpatient visit numbers

Outcomes from the Polyclinic Visit numbers of sixty patients and four different centers have been obtained in 3 different time frames below.

The Table 4 has been created according to the Outpatient visit numbers of 60 patients below.

The mean of outpatient visit numbers was 5,25 after 6 months from DBS and, 8,95 after 1 year from DBS.

### Cost outcome analysis

Mean drug, outpatient and surgical cost data have been analyzed for all four centers and sixty patients. All cost data have been

**Table 2:** UPDRSIII outcomes for 60 patients with mean, standard deviation and confidence interval statistical values.

	UPDRS III (A: 1 year before DBS)	UPDRS III (B: 6 months after DBS)	UPDRS III (C: 1 year after DBS)
Mean	32,77	18,27	16,32
Standard Dev	10,50	10,34	10,56
Confidence Interval	2,64	2,60	2,65
	A-B Difference	A-C Difference	B-C Difference
P	<0,001	<0,001	<0,001

**Table 3:** Hoehn & Yahr outcomes for 60 patients with mean, standard deviation and confidence interval statistical values.

	HOEHN YAHR A	HOEHN YAHR B	HOEHN YAHR C
Mean	2,98	1,58	1,27
Standart Dev	0,77	0,54	0,43
Confidence Interval	0,19	0,14	0,11
p value	p<0,001	p<0,001	p<0,001

**Table 4:** Analysis of 60 patients outpatient visit number outcomes.

	Outpatient Visit Numbers A	Outpatient Visit Numbers B	Outpatient Visit Numbers C
Mean	3,88	5,25	8,95
Standart Dev	4,15	2,49	4,17
Confidence Interval	1,16	0,72	1,22
		A-B Difference	A-C Difference
P		0,02	<0,001

verified as a significant by Wilcoxon, Friedmann and One Sample Kolmogorov Test analysis.

## 2 Mean drug cost analysis

Outcomes of sixty patients' drug usage cost have been obtained in 3 different time frames below.

- a. 1 year before DBS surgery
- b. 6 months after DBS surgery
- c. 1 year after DBS surgery

The **Table 5** has been created according to the average drug cost changes of 60 patients below.

The significant decrease in the mean drug cost after 6 months and 1 year from DBS surgery was shown in **Table 5**.

## Outpatient cost analysis

Outcomes of sixty patients' outpatient cost have been obtained in 3 different time frames below.

- A) 1 year before DBS surgery
- B) 6 months after DBS surgery
- C) 1 year after DBS surgery

The **Table 6** has been created according to the outpatient cost changes of 60 patients below.

The significant increase in outpatient cost after 6 months and 1 year DBS was shown in **Table 6**.

## The mean surgery cost analysis

In all four hospitals, the cost of the surgery and the payment for DBS device was constant and same numbers and therefore the total cost was 58.079,82 TL per patient.

## The cost effectiveness analysis

In the cost-effectiveness analysis, the costs of drug treatment and one-year period of after the DBS surgical treatment were

**Table 5:** Mean Drug Cost Outcome for 60 patients.

	Durg Cost A (TL)	Durg Cost B (TL)	Durg Cost C (TL)
Mean	12.260,17	3.710,27	5.515,62
Standart Dev	3.625,06	1.325,65	2.306,77
Confidence Interval	10.915,70	3.224,84	3.350,87
	A-B Difference	A-C Difference	B-C Difference
P	<0,001	<0,001	<0,001

**Table 6:** The Mean Outpatient visit cost of 60 patients.

	Outpatient Cost A (TL)	Outpatient Cost B (TL)	Outpatient Cost C (TL)
Mean	515,83	1.626,07	2.676,82
Standart Dev	348,45	1.398,82	2.137,90
Confidence Interval	88,17	353,94	540,95
	A-B Difference	A-C Difference	B-C Difference
P	<0,001	<0,001	<0,001

compared and calculated. Hoehn and Yahr and UPDRS III scores have been obtained one-year before and one-year after the DBS surgical treatment. Two different group of Monte Carlo Analyses has been performed for each comparing scenario by calculated standard deviation of the outcomes.

## Analysis in terms of UPDRS III outcomes

The drug usage and DBS surgery cost have been compared before and after DBS surgery and evaluated with UPDRSIII outcomes for all sixty patients.

**Table 7** has been created with ICER (incremental cost effectiveness ratio) calculation according UPDRSIII outcome in terms of drug usage and DBS surgery cost.

In the first year after the comparison, the DBS cost is higher than drug cost. But the additional cost ratio (ICER) based on UPDRS III change after DBS surgery is 2.122,13 TL. The difference in the total UPDRSIII scale is 17.37 in one year. This UPDRSIII decrease has showed clinical improvement with DBS surgery and this surgery has cost benefit outcome (**Table 7**).

## Analysis in terms of Hoehn and Yahr outcomes

The drug usage and DBS surgery cost have been compared before and after DBS surgery and evaluated with Hoehn and Yahr outcomes for all sixty patients.

**Table 8** has been created with ICER (incremental cost effectiveness ratio) calculation according Hoehn and Yahr outcome in terms of drug usage and DBS surgery cost.

In the first year after the comparison, the DBS cost is higher than drug cost. But the additional cost ratio (ICER) based on Hoehn and Yahr change after DBS surgery is 25.598,22 TL. The difference in the total Hoehn and Yahr scale is 1.44 in one year. This Hoehn and Yahr decrease has showed clinical improvement with DBS surgery and this surgery has cost benefit outcome (**Table 8**).

## Discussion

We evaluated cost effectiveness and clinical outcome of DBS surgery in the following first year in sixty patient from four university hospitals. The significant decrease in UPDRS III and Hoehn&Yahr from 24,7 to 7,4 and the from 2,57 to 1,53

**Table 7:** One-Year Markov Simulation of DBS and Drug Costs based on 60 patients' UPDRSIII Outcome.

	Drug Therapy	DBS + Drug Therapy
Cost (TL)	21.218,39	58.079,82
UPDRSIII Outcome	24,47	7,1

**Table 8:** One-Year Markov Simulation of DBS and Drug Costs based on 60 patients' Hoehn & Yahr Outcome.

	DBS+Drug Therapy	Drug Therapy
Cost (TL)	58.079,82	21.218,39
Hoehn & Yahr Outcome	1,13	2,57
Cost Difference (TL)	Hoehn Yahr Difference	1 Hoehn Yahr Decrease Cost / ICER (TL)
36.861,43	1,44	25.598,22

respectively was observed before and after one-year DBS surgery. Similarly in the past a randomized controlled clinical study, DBS surgery and drug therapy have been compared and DBS was clinically more effective than the best drug treatment in the first six-month period. As far as for the clinical rating scales UPDRSIII and Hoehn & Yahr are preferred likely with the study in 2018 [44]. To broaden our perspective in assessing clinical outcomes, other clinical assessment tools such as UDPRSIV, Schwab England and PDQ39 might have been used. Since the data were retrospectively obtained from four different university hospitals, we could not assess health related quality of life, routine daily, activities, and drug related complication of the patient.

As expected in STN DBS surgery equivalent Levodopa doses of patients significantly decreased in the first year after DBS which is well known from the literature [45]. The drug usage dose decreased 53.83% and 57,1% in six months and one year DBS therapy, respectively.

The statistical methods Wilcoxon, Friedman and One Sample Kolmogorov Analysis which have been used for clinical and cost data verification, were also used in literature for 41 and 62 number of patients' DBS literature studies [46,47].

The significant decreases in UPDRSIII and Hoehn & Yahr scores

reflecting the clinical improvement of sixty patients, were not concorded with the number of outpatient and the cost of follow up visits. DBS therapy requires more outpatient visit as suggest by the literature in 2016 which has created the DBS device follow up protocol up to two years as a Toronto Western Hospital Algorithm [48].

The comparison cost outcome in our study between DBS and best medical treatment (drug therapy) could not reach the cost effectiveness result in one-year term. However, the DBS therapy has cost benefit results and our study might be evaluated and continued for long term in order to reach cost effectiveness results like the update literatures [49,50].

In conclusion, clinical improvement may not be accompanied by cost effectiveness in short term follow up after DBS surgery which necessitate prospective long term follow up multi-central studies.

## Conclusion

The comparison cost outcome in our study between DBS and best medical treatment (drug therapy) could not reach the cost effectiveness result in one-year term. However, the DBS therapy has cost benefit results and our study might be evaluated and continued for long term in order to reach cost effectiveness results like the update literatures.

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