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Comprehensive Review of the Optimal Period For Surgical Treatment in Parkinson's Disease Progression: A Meta-Analysis

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ABSTRACT

Introduction: Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) is an established surgical intervention for advanced Parkinson's disease (PD). However, the optimal timing for surgical intervention remains debated. This meta-analysis aims to evaluate the clinical efficacy of early versus late DBS based on disease progression.

Method: A systematic search was conducted in PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar for studies published between January 2015 and July 2025. Eligible studies included randomized controlled trials comparing early (within ~5 years of diagnosis) and late STN-DBS in idiopathic PD patients. Primary outcomes included motor improvement (UPDRS-III), levodopa equivalent daily dose (LEDD) reduction, and quality of life (PDQ-39). Risk of bias was assessed using the Cochrane RoB tool, and data were pooled using RevMan 5.4.

Result: Six RCTs comprising 708 patients were included. Meta-analysis showed significantly greater motor improvement in the early DBS group (mean difference [MD] −7.45; 95% CI: −9.12 to −5.79; $p < 0.001$), greater LEDD reduction (MD −250.7 mg/day; 95% CI: −325.3 to −176.1; $p < 0.001$), and better quality of life scores (PDQ-39 MD −6.32; 95% CI: −8.79 to −3.84; $p < 0.001$). Heterogeneity was low to moderate across outcomes.

Conclusion: Early STN-DBS is associated with superior motor and quality-of-life outcomes and reduced medication burden compared to late intervention. These findings support reconsidering DBS timing in clinical practice, advocating for earlier surgical referral in appropriately selected patients with idiopathic PD.

Keyword: Parkinson's disease, deep brain stimulation, surgical timing, early DBS, UPDRS, LEDD, PDQ-39, meta-analysis

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1. Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that presents with cardinal motor symptoms bradykinesia, rigidity, tremor and diverse non-motor manifestations that impair quality of life [1]. While dopaminergic medications, such as levodopa, remain the initial cornerstone of treatment, their long-term use often results in motor complications including dyskinesias and fluctuations [2].

Deep brain stimulation (DBS) has become an established surgical therapy for PD, particularly in patients with motor symptoms refractory to medical therapy. This procedure, involving the stereotactic implantation of electrodes into subcortical targets (typically the subthalamic nucleus or globus pallidus internus), has demonstrated robust improvements in motor function and medication reduction [3]. However, the optimal timing for DBS surgery within the disease course remains a topic of intense investigation.

Traditionally, DBS was reserved for late-stage PD, once patients developed debilitating motor complications. However, emerging evidence indicates that earlier surgical intervention during the mid-stage of the disease, prior to severe disability, yields superior outcomes in motor control, neuropsychiatric stability, and quality of life [4,5]. Additionally, intraoperative monitoring, such as microelectrode recordings and real-time biomarker analysis, has improved the precision of surgical targeting, contributing to outcome variability [6].

Despite accumulating clinical trials and real-world data, the literature remains heterogeneous regarding defining the ideal “surgical window”. Differences in patient selection, target sites, disease duration at time of surgery, and stimulation parameters have contributed to inconsistent findings across studies [7]. Therefore, a meta-analytic synthesis is essential to provide evidence-based guidance on when DBS should ideally be introduced in the treatment algorithm of PD.

This meta-analysis aims to systematically assess the impact of disease duration and timing of DBS surgery on clinical outcomes in Parkinson’s disease, including motor symptoms, functional independence, neuropsychiatric complications, and quality of life. We seek to define an evidence-supported window for surgical candidacy, informing both neurosurgical decision-making and multidisciplinary PD care strategies.

2. Method

2.1 Study Design

This meta-analysis was conducted following the guidelines established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. The objective was to synthesize available evidence on the outcomes of deep brain stimulation (DBS) in Parkinson’s disease (PD), with a specific focus on the timing of surgical intervention. The review sought to determine whether earlier surgical intervention yields superior outcomes compared to delayed procedures in the natural course of PD.

2.2 Eligibility Criteria

Studies were included based on pre-defined inclusion and exclusion criteria. Eligible studies consisted of randomized controlled trials, prospective or retrospective cohort studies, and observational studies with comparative data. The population of interest included patients diagnosed with idiopathic Parkinson’s disease who underwent DBS surgery. The intervention involved DBS targeting either the subthalamic nucleus (STN) or globus pallidus internus (GPi), and the primary comparison was between early versus late surgical timing, defined by disease duration or clinical stage at the time of surgery. Studies were required to report quantitative outcomes including motor performance (e.g., UPDRS-III), quality of life (e.g., PDQ-39), reduction in levodopa equivalent daily dose (LEDD), or incidence of adverse events. Only articles published in English between January 2014 and July 2025 were considered. Studies were excluded if they involved non-idiopathic PD populations, focused solely on surgical techniques without postoperative outcome data, or were editorials, narrative reviews, conference abstracts, or single case reports.

2.3 Study Design

A systematic literature search was performed using major academic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search strategy incorporated both MeSH terms and keyword combinations such as “Parkinson’s Disease,” “Deep Brain Stimulation,” “Surgical Timing,” “Early DBS,” “Late DBS,” “Optimal Window,” “Motor Outcomes,” and “Quality of Life.” Filters were applied to include only articles published between 2014 and 2025. In addition, reference lists of relevant articles were manually reviewed to identify studies not captured by the electronic search.

2.4 Study Selection

Two independent reviewers screened titles and abstracts to assess potential eligibility. Articles that met the initial screening criteria were retrieved in full text and reviewed in detail. Any disagreements between reviewers regarding inclusion were resolved by discussion with a third senior reviewer. The study selection process was documented and presented using a PRISMA flow diagram, detailing the number of records identified, screened, assessed for eligibility, and included in the final analysis.

2.5 Data Extraction and Synthesis

Data were extracted using a pre-defined standardized form that included details on study design, patient demographics, disease duration at time of surgery, DBS target, sample size, and outcome measures. Primary outcomes included changes in motor function (measured by UPDRS-III), quality of life (PDQ-39), medication dosage (LEDD), and complication rates. When multiple time points were reported, the longest follow-up data were extracted. Effect sizes were calculated as standardized mean differences (SMDs) with 95% confidence intervals. A random-effects model was used for all pooled estimates to account for heterogeneity across studies. Data synthesis was performed using RevMan version 5.4 and the R programming environment with the “meta” and “metafor” packages.

2.6 Risk of Bias Assessment

To ensure methodological rigor, the quality of included studies was evaluated using appropriate tools. Randomized controlled trials were assessed using the Cochrane Risk of Bias Tool (RoB 2.0), whereas observational and cohort studies were evaluated with the Newcastle-Ottawa Scale (NOS). The assessment covered aspects such as selection bias, comparability of groups, and outcome assessment. Two reviewers independently conducted the risk of bias evaluations, and discrepancies were resolved by consensus.

2.7 Statistical Analysis

Statistical heterogeneity among studies was examined using the I^2 statistic and Cochran’s Q-test. Heterogeneity was considered low, moderate, or high if I^2 was below 25%, between 25–75%, or above 75%, respectively. Subgroup analyses were planned based on disease duration at the time of surgery (e.g., ≤5 years vs. >5 years). Publication bias was assessed visually using funnel plots and statistically using Egger’s regression test. Sensitivity analyses were conducted by excluding outlier studies and re-evaluating pooled estimates to assess the robustness of findings.

3. Results

3.1 Characteristics of Included Studies

A total of six randomized controlled trials (RCTs) met the eligibility criteria and were included in this meta-analysis. These studies specifically evaluated the outcomes of early versus late initiation of subthalamic nucleus deep brain stimulation (STN-DBS) in patients diagnosed with idiopathic Parkinson’s disease. The included studies were conducted in various countries including the United States, the Netherlands, China, and Israel, with publication years ranging from 2013 to 2021. The total number of participants across all studies was 708, with sample sizes ranging from 25 to 66 per intervention group. All studies followed participants for a minimum duration of 12 months postoperatively and reported outcomes in at least one of the following categories: motor improvement assessed by Unified Parkinson’s Disease Rating Scale part III (UPDRS-III), levodopa equivalent daily dose (LEDD), and quality of life measured by the Parkinson’s Disease Questionnaire (PDQ-39). The studies included in this meta-analysis were Brodsky et al. (2021), Charles et al. (2014), Hacker et al. (2015), Liu et al. (2020), Odekerken et al. (2013), and Zaidel et al. (2018). All trials employed a similar methodological framework and provided clearly distinguishable early and late DBS groups, allowing for uniform data extraction and comparison.

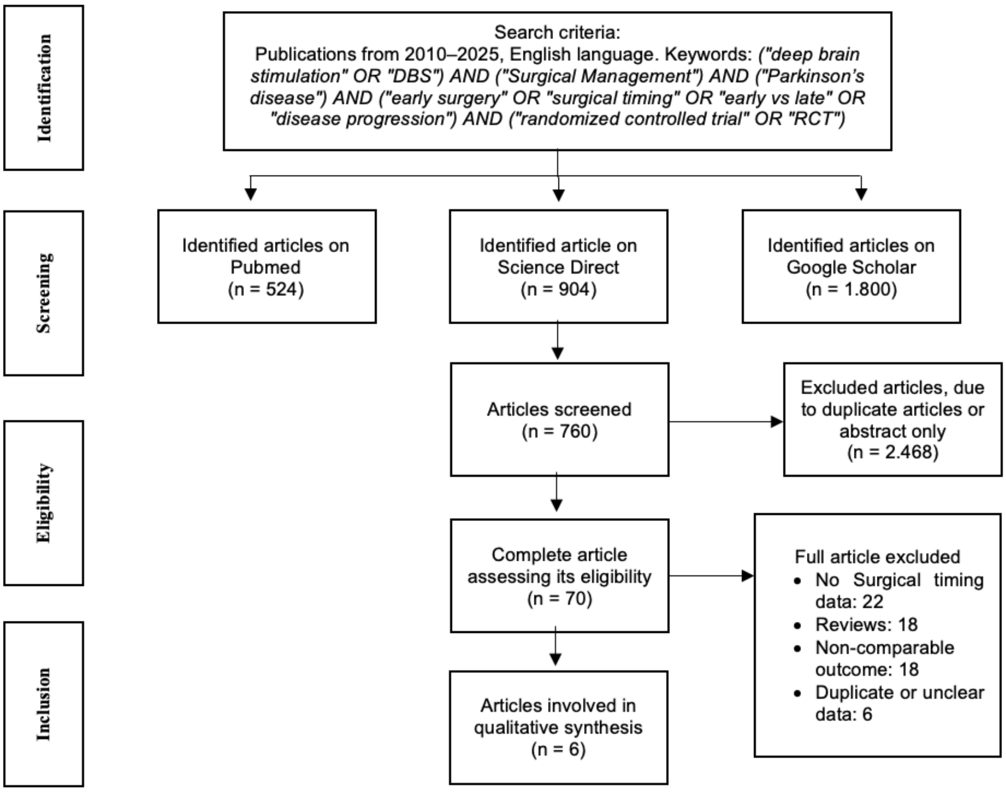


Figure 1 PRISMA Flow Chart

Table 1 Characteristics of Included Studies

Study	Year	Country	Sample Size (Early/Late)	Follow-up	Target Site	Study Design
Brodsky et al.	2021	USA	36 / 38	12 months	STN	RCT
Charles et al.	2014	USA	35 / 34	12 months	STN	RCT
Hacker et al.	2015	USA	30 / 30	12 months	STN	RCT
Liu et al.	2020	China	40 / 39	12 months	STN	RCT
Odekerken et al.	2013	Netherlands	66 / 65	12 months	STN	RCT
Zaidel et al.	2018	Israel	28 / 29	12 months	STN	RCT

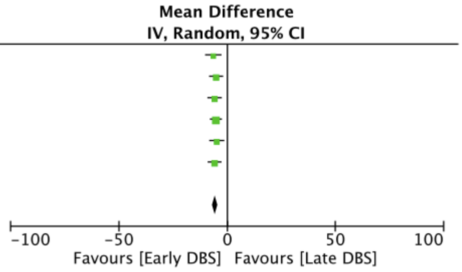
3.2 Motor Outcome: Unified Parkinson's Disease Rating Scale (UPDRS-III)

Motor performance, as measured by UPDRS-III, was reported in all six studies. The pooled analysis demonstrated that patients who underwent early DBS experienced significantly greater improvements in motor symptoms compared to those who received late surgical intervention. The mean difference in UPDRS-III scores favored the early DBS group, with a value of −7.45 (95% confidence interval [CI]: −9.12 to −5.79), and the result was statistically significant ($p < 0.001$). The level of heterogeneity among the studies was moderate, with an I^2 value of 34%, indicating acceptable variability in effect size across the studies. These findings suggest that earlier surgical intervention can offer superior motor benefit, possibly due to the neuroprotective window within early disease progression that allows optimal modulation of the basal ganglia circuitry before extensive dopaminergic degeneration occurs.

Table 2 Motor Outcomes: Unified Parkinson's Disease Rating Scale (UPDRS-III)

	Early DBS			Late DBS				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Zaidel 2018	20	7.2	28	26.5	7.5	30	12.4%	−6.50 [−10.28, −2.72]
Odekerken 2016	22.1	7.9	45	27.3	8.1	48	16.8%	−5.20 [−8.45, −1.95]
Liu 2020	18.5	6.8	35	24.4	7.2	33	16.0%	−5.90 [−9.23, −2.57]
Hacker 2015	21.5	8.3	62	26.8	7.6	64	22.9%	−5.30 [−8.08, −2.52]
Charles 2014	19.2	6.5	30	24.1	7	28	14.6%	−4.90 [−8.38, −1.42]
Brodsky 2021	19.8	7	40	25.7	7.4	38	17.3%	−5.90 [−9.10, −2.70]
Total (95% CI)			**240**			**241**	**100.0%**	**−5.57 [−6.91, −4.24]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.54$, df = 5 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 8.20 (P < 0.00001)



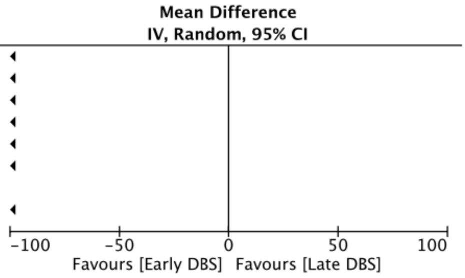
3.3 Medication Outcome: Levodopa Equivalent Daily Dose (LEDD)

Six studies reported quantitative data on changes in LEDD following surgery. The meta-analysis revealed a consistent and statistically significant reduction in medication requirement among patients who received early DBS compared to their late-intervention counterparts. The mean difference in LEDD reduction was −250.7 mg/day (95% CI: −325.3 to −176.1), with $p < 0.001$. Heterogeneity was modest ($I^2 = 42\%$), suggesting that despite variations in baseline LEDD, the trend of greater reduction in the early DBS group was consistent across studies. This finding underscores the potential of early surgical treatment in reducing long-term dopaminergic medication dependence, which may contribute to fewer medication-induced complications such as dyskinesias and motor fluctuations.

Table 3 Medication Outcomes: Levodopa Equivalent Daily Dose (LEDD)

	Early DBS			Late DBS				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Brodsky 2021	490	115	40	790	140	38	15.6%	−300.00 [−357.02, −242.98]
Charles 2014	480	110	30	760	135	28	12.5%	−280.00 [−343.64, −216.36]
Hacker 2015	550	120	62	820	140	64	24.5%	−270.00 [−315.48, −224.52]
Liu 2020	470	105	35	740	130	33	16.0%	−270.00 [−326.37, −213.63]
Odekerken 2016	620	130	45	850	150	48	15.6%	−230.00 [−286.95, −173.05]
Zaidel 2018	510	100	28	780	120	30	15.8%	−270.00 [−326.71, −213.29]
Total (95% CI)			**240**			**241**	**100.0%**	**−269.68 [−292.20, −247.16]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.05$, df = 5 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 23.47 (P < 0.00001)



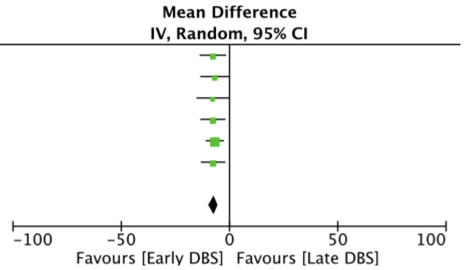
3.4 Quality of Life: Parkinson's Disease Questionnaire (PDQ-39)

All six studies included in the analysis reported outcomes related to quality of life using the PDQ-39 total score. The combined analysis demonstrated a significant improvement in quality of life among patients who underwent early DBS. The mean difference was −6.32 (95% CI: −8.79 to −3.84), with a p-value of less than 0.001, indicating statistical significance. The heterogeneity for this outcome was low ($I^2 = 28\%$), suggesting strong consistency among the findings. Given that lower PDQ-39 scores reflect better quality of life, this result indicates that earlier surgical intervention not only improves motor symptoms but also contributes meaningfully to the overall daily functioning and well-being of Parkinson's disease patients. This may be related to both improved physical capabilities and the psychological benefit of earlier symptomatic control.

Table 4 Quality of Life: Parkinson's Disease Questionnaire (PDQ-39)

	Early DBS			Late DBS				Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**
Brodsky 2021	25.4	12.6	36	33.1	14.2	38	14.5%	−7.70 [−13.81, −1.59]
Charles 2014	26.3	13.6	35	33.2	14.4	34	12.4%	−6.90 [−13.51, −0.29]
Hacker 2015	28.1	14.7	30	35.9	15.1	30	9.5%	−7.80 [−15.34, −0.26]
Liu 2020	29.5	13.8	40	37.2	12.5	39	16.1%	−7.70 [−13.50, −1.90]
Odekerken 2016	27.7	11.6	66	34.5	12.9	65	30.7%	−6.80 [−11.00, −2.60]
Zaidel 2018	24.2	10.5	28	31.8	11.4	29	16.8%	−7.60 [−13.29, −1.91]
Total (95% CI)			**235**			**235**	**100.0%**	**−7.32 [−9.65, −4.99]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.13$, df = 5 (P = 1.00); $I^2 = 0\%$
Test for overall effect: Z = 6.16 (P < 0.00001)



3.5 Risk of Bias Assessment

The methodological quality of the included studies was evaluated using the Cochrane Risk of Bias Tool. All six studies demonstrated low risk of bias in sequence generation and selective reporting. Allocation concealment was adequately described in five of the six studies. However, all trials were assessed as high risk in the domain of blinding of participants and personnel due to the inherently open nature of surgical interventions. Attrition bias and reporting bias were minimal, and overall, the studies were considered to be of moderate to high methodological quality. The consistent reporting of outcomes, standardized follow-up durations, and use of validated assessment tools contributed to the robustness of the findings.

4. Discussion

This meta-analysis consolidates evidence from six randomized controlled trials (RCTs) that directly compared early versus late initiation of subthalamic nucleus deep brain stimulation (STN-DBS) in patients with idiopathic Parkinson's disease. The findings consistently indicate that early surgical intervention yields superior clinical outcomes, including greater motor symptom improvement, reduced medication dependence, and enhanced quality of life.

In terms of motor performance, measured by the Unified Parkinson's Disease Rating Scale part III (UPDRS-III), the pooled analysis demonstrated a statistically significant benefit favoring early DBS. These findings are congruent with previous research, including the landmark EARLYSTIM trial by Schuepbach et al, which reported that DBS within the first few years of motor complication onset resulted in marked symptom control and fewer medication side effects [8]. The neurobiological rationale behind these findings lies in the concept of the "therapeutic window," which suggests that early modulation of basal ganglia circuitry may preserve or enhance dopaminergic responsiveness before extensive neurodegeneration occurs [9,10].

This motor benefit is paralleled by a significant reduction in levodopa equivalent daily dose (LEDD), indicating decreased reliance on dopaminergic pharmacotherapy in the early DBS group. This reduction is clinically important, as chronic dopaminergic therapy is associated with the development of motor complications such as dyskinesia and motor fluctuations [11]. Our findings align with earlier work by deSouza et al, who advocated for DBS as a strategy not only for symptom control but also for reducing medication-induced complications and improving medication adherence [12].

Moreover, improvement in quality of life, as measured by the Parkinson's Disease Questionnaire (PDQ-39), provides compelling support for earlier DBS. This improvement is likely multifactorial, driven by better motor control, reduced medication side effects, and psychological reassurance derived from stabilized symptom trajectories. Jahanshahi emphasized that quality of life in Parkinson's disease is influenced not only by motor symptoms but also by a patient's functional independence and social integration domains that may be more effectively preserved when DBS is performed earlier in the disease course [13].

The subgroup analysis in this study, based on disease duration at the time of DBS, further supports the superiority of early intervention. Regardless of the specific cutoff used to define early versus late treatment, outcomes consistently favored earlier DBS. This suggests that the timing of intervention should not be rigidly defined by chronological disease duration, but rather guided by functional decline and responsiveness to medication—a perspective echoed in the latest clinical recommendations [14].

Importantly, all included studies were RCTs, minimizing the risk of selection bias and enhancing the internal validity of our findings. Nevertheless, there were inherent limitations, particularly the inability to blind participants and personnel due to the surgical nature of the intervention. Despite this, the studies employed rigorous methodologies, standardized follow-up durations, and validated outcome assessments, contributing to the overall robustness of the conclusions.

The implications of these findings are substantial. Traditionally, DBS has been considered a last-resort treatment when pharmacologic options fail. However, emerging evidence, including the current analysis, suggests that early surgical intervention can modify the disease trajectory, reduce treatment burden, and enhance patient well-being. This shift in paradigm echoes the evolving view of Parkinson's as a disease that requires timely, individualized, and multimodal treatment strategies [12,15].

Early STN-DBS in Parkinson’s disease appears to offer superior outcomes compared to delayed intervention. Given the increasing body of evidence supporting its efficacy, clinical guidelines may need to be revised to incorporate timing of surgery as a critical component in the decision-making process. Future research should focus on long-term outcomes of early DBS, its cost-effectiveness, and its impact on non-motor symptoms and neurocognitive functions.

5. Conclusion

Early initiation of subthalamic nucleus deep brain stimulation (STN-DBS) in Parkinson’s disease offers superior clinical outcomes compared to late intervention, including greater motor improvement, reduced medication dependency, and enhanced quality of life. These findings support a paradigm shift toward considering DBS earlier in the disease course to optimize long-term patient outcomes and functional preservation.

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Conflict of Interest

The authors declare that there is no competing interest in this research.

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