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Treating Parkinson's Disease: Comparing the clinical effectiveness of deep brain stimulation and pramipexole

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Abstract

Parkinson's Disease is among the most common neurodegenerative diseases with over ten million cases worldwide. By comparing the clinical effectiveness of treatment methods like deep brain stimulation and pramipexole through use of the United Parkinson's Disease Rating Scale (UPDRS), clinicians are better equipped to recommend a treatment method to improve the patient's quality of life, and therapeutics developers can better assess the shortcomings and strengths of each treatment. The UPDRS is a survey that rates Parkinson's Disease symptoms on a scale of 0 to 4. Higher UPDRS scores correlate with more severe symptoms. To evaluate deep brain stimulation and pramipexole, ninety-two studies were screened using filters like the age of Parkinson's Disease patients (50+), type of treatment received, and UPDRS scores. Ultimately, twenty-eight studies were deemed eligible for analysis. Of particular interest were UPDRS I and III scores as they correlate to mentation, mood, and behavior and motor examination, respectively. Treatments like deep brain stimulation and pramipexole attempt to reduce the severity of symptoms experienced by patients and lower their UPDRS score. While both treatments failed to lower the severity of cognitive symptoms, pramipexole proved to be more effective as it had a mean change in the UPDRS I score 12.725 times lower than deep brain stimulation. Motor symptoms improved when either pramipexole or deep brain stimulation was

administered; however, deep brain stimulation presented a mean change in the UPDRS III score 4.75 times lower than pramipexole, indicating that it suppressed motor symptoms more effectively.

Highlights

- Effectiveness of specific treatments for Parkinson's have not been studied extensively
- Exclusively assessed studies using the United Parkinson's Disease Rating Scale (UPDRS)
- Both treatments improved motor symptoms according to the change in UPDRS III scores
- More treatment-specific reviews would help developers, clinicians, and patients

1. Introduction

In the United States alone there are approximately 930,000 Parkinson's Disease diagnoses and the number is projected to increase to 1.2 million by 2030 [1,2]. While men and people living in urban areas are more likely to develop Parkinson's Disease, everyone becomes more susceptible as they age [1,3]. The United Parkinson's Disease Rating Scale (UPDRS) created by the Movement Disorder Society has been established as the current standard for objectively assessing Parkinson's Disease Symptoms. Quantification of the UPDRS score is determined by a combination of observations and patient reflection [4].

There have been multiple studies that have suggested the effectiveness of either deep brain stimulation or pramipexole using the UPDRS [5,6,7,8,9]. A few studies have even compared the UPDRS scores of deep brain stimulation and standard medical treatment [10,11,12]. However, a clear comparison between two singular treatment options for Parkinson's patients remains unknown.

With a growing number of Parkinson's Disease patients around the world, it is important to measure the clinical effectiveness of available treatment options in an effort to identify which treatments will have the greatest chance to improve both life expectancy and quality of life. This paper aims to address the following question: how are the motor and cognitive symptoms, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS), of elderly patients afflicted with Parkinson's Disease affected when deep brain stimulation is administered compared with the standard medication pramipexole?

This review examines the clinical effectiveness of both deep brain stimulation and pramipexole in treating motor and cognitive symptoms of patients afflicted with Parkinson's Disease. The majority of the current knowledge about the efficacy of each of these treatment methods is from clinical trials testing deep brain stimulation devices and surveys distributed to patients taking pramipexole for various lengths of time. This review uses the combined knowledge of these available data sources and identifies a standard measure of clinical effectiveness to analyze how each treatment may affect motor and cognitive symptoms of Parkinson's Disease patients. The review presents a comprehensive comparison of the two treatments, and follows a structure derived from the UPDRS, which is a multi-part survey that evaluates symptoms of Parkinson's Disease. Parts I and III of the UPDRS are of particular interest as they represent the sections of the survey that reflect mentation, behavior, and mood, and motor examination respectively. In addition to the analysis of the clinical effectiveness of deep brain stimulation and pramipexole, the review also proposes future directions for research.

2. Methods

2.1 Initial Search Methods and Final Selection Criteria

The specific terms derived from the research question and used to search for studies include “Parkinson’s Disease treated with deep brain stimulation (DBS)” and “Parkinson’s Disease treated with pramipexole.” The terms were searched for in the titles and abstracts of studies and systematic reviews within the ClinicalTrial.gov, PubMed, and NCBI databases. The filters “text availability: free full text,” “study results: with results,” “language: English,” “species: human,” and “article types: clinical study, risk assessment, randomized controlled trial, meta-analysis, and systematic review” were applied to each database accordingly. Initial search methods yielded ninety-two results.

The final selection criteria (**Table 1**) was then used to further refine the studies used for the systematic review.

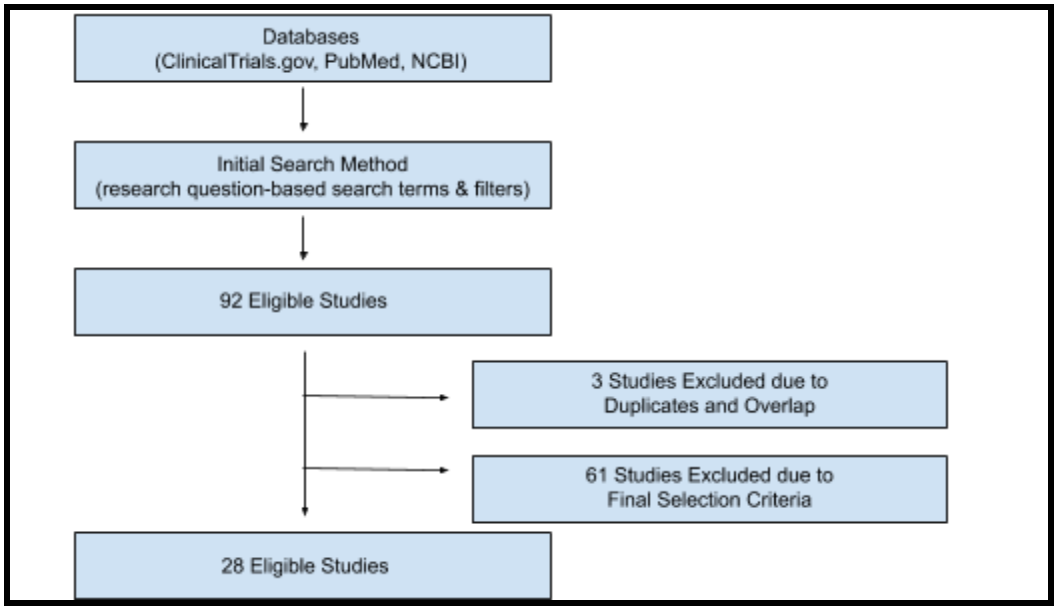
Table 1: Final Selection Criteria

Population	Patients of age 50+ and diagnosed with Parkinson’s disease
Intervention	Deep brain stimulation (a surgically implanted device)
Comparator	Pramipexole (a standard medication-based treatment)
Outcomes	Clinical effectiveness • Reduced motor symptoms (UPDRS Part III) • Reduced cognitive symptoms (UPDRS Part I)
Study Design	Clinical studies, systematic reviews, meta-analyses, and randomized controlled trials

The search and selection process (**Fig. 1**) excluded studies that failed to meet the standards outlined by the final selection criteria. Similarly, duplicate and overlapping studies were removed as well. As a result, twenty eight studies with a total of 1,264 deep brain

stimulation patient samples and 6,519 pramipexole patient samples were eligible for inclusion and analysis [5,6,7,8,9,10, 11,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33].

Fig. 1: Search and Selection Process



2.2 Organization, Variables, and Data Cleaning

Systematic organization was established through citation and tagging features within Zotero. All the data collected was then organized into two smaller data sets each containing the outcome variable, the applicable UPDRS score (Part I or Part III), and the two predictor variables, deep brain stimulation and pramipexole. Separating based on the Part of the UPDRS score allows for closer analysis of how each treatment affects motor and cognitive symptoms individually.

After being sorted into the appropriate data set, the UPDRS scores were divided based on the corresponding treatment method used, forming two columns (one representing deep brain stimulation and the other representing pramipexole). The data sets were then screened for missing values. Observations with missing values were removed from the data set as no reasonable assumptions could be made. Each data set was then saved as a comma-separated

values file (.csv) and read into R Studio. Using R Studio, summary statistics as well as box plots were generated to easily identify outliers within the data. The outliers were noted, but not removed from the data sets.

2.3 Statistical Tests and Assumptions

A two-sample t-test was most appropriate as the data sets contained two separate populations (deep brain stimulation patients and pramipexole patients).

All the two-sample t-tests were conducted with the significance level set at $\alpha = 0.05$. The significance tests were performed and then analyzed to determine which of the formal hypotheses would be accepted: the null hypothesis-there is no statistically significant difference between the true means of the Unified Parkinson's Disease Rating Scale scores of patients receiving deep brain stimulation and patients receiving pramipexole-or the alternative hypothesis-there is a statistically significant difference between the true means of the Unified Parkinson's Disease Rating Scale scores of patients receiving deep brain stimulation and patients receiving pramipexole.

Assumptions related to the two-sample t-test include: random sampling for both samples, a continuous outcome variable, samples that are independent, the outcome variable being normally distributed for both samples, and the variances of the two samples are similar. The design of the studies were checked for random sampling during the search and selection process. The UPDRS score was selected as the outcome variable and was determined to be continuous as the score can be any number or fraction of a number. The samples were verified as independent due to each patient afflicted with Parkinson's Disease only receiving one of the treatments (deep brain stimulation or pramipexole). Finally, both normality and variances were checked using R

Studio. Normally distributed data was checked for through producing a histogram, while utilization of the function var() verified that the variances were similar.

3. Results

3.1 UPDRS Scores

The mean changes in the UPDRS scores **(Table 2)** show that on average patients on either treatment experienced slightly worsened cognitive symptoms and improved motor symptoms.

Table 2: Mean Change in UPDRS Scores

UPDRS Part	Treatment	Mean Change in UPDRS Score*
I	Deep Brain Stimulation	0.509
	Pramipexole	0.040
III	Deep Brain Stimulation	-8.816
	Pramipexole	-1.857

*A negative change in the UPDRS Score indicates that conditions have improved and symptoms are less severe

3.2 T-tests

The results of the t-tests **(Table 3)** show that the p-values for each part of the UPDRS were less than the 0.05 set significance value. The results of the statistical test for UPDRS I are $r(45) = 4.99$, $p < 0.0005$ and the results of UPDRS III are $r(61) = -6.09$, $p < 0.0005$. Additionally, the intervals show the range in which we are 95% confident that the true population mean lies.

Table 3: Confidence Intervals and P-Values

UPDRS Part	95% Confidence Interval Lower Margin	Upper Margin	P-Value	Degrees of Freedom
I	0.285	0.673	9.597×10^{-6}	45
III	-14.742	-7.458	8.078×10^{-8}	61

4. Conclusion

4.1 Results in Context

For both treatments the mean change in the UPDRS I score was positive, indicating that on average symptoms relating to cognition became slightly more severe over the course of the study. While the mean change in the scores was less than one point, the positive trend towards increased cognitive symptoms remains. The p-value of less than 0.05 provides evidence to reject the null hypothesis and favor the alternative hypothesis that there is a statistically significant difference between the true means of the UPDRS I scores. Because the change in the UPDRS I score was less for those receiving pramipexole, pramipexole is the better treatment option for patients looking to specifically manage their cognitive symptoms. The assessment in favor of pramipexole is consistent with individual existing studies, which cite the increased prevalence of apathy in patients receiving deep brain stimulation and pramipexole's high affinity for D3 receptors and its ability to fully stimulate dopamine receptors leading to psychiatric benefits [37,38].

The UPDRS III scores reflect patients' motor examinations [39]. For both treatments the mean change in the UPDRS III scores were negative, indicating that on average motor symptoms were improved over the course of the study. Like the UPDRS I t-test, the t-test for the UPDRS III scores also indicated statistically significant results, leading to the rejection of the null

hypothesis. When comparing the UPDRS III scores, pramipexole only offered limited improvement of motor symptoms, meaning that for patients struggling with motor symptoms, deep brain stimulation treatment has greater potential to deliver significant improvement. The results, which favor deep brain stimulation, are consistent with other studies that point out pramipexole is primarily used to address restless leg syndrome and that deep brain stimulation's ability to silence the abnormal electrical activity in the basal ganglia allows for motor based actions to progress as normal [38,40].

4.2 Limitations

The review can only be as reliable as the data and studies that it uses. While the search and selection criteria were strictly followed, it can be difficult to create standards across studies with different research methods and interests. The lack of studywide standards results in greater variability. The data collected for this review was across twenty-eight different studies, all with different goals and methods, which limits the reliability of the results. Despite the potentially varied data, the combination of statistically significant t-tests results and mean changes in UPDRS scores consistent with existing research suggests that feasible conclusions can still be drawn from the results.

Furthermore, exclusively using the UPDRS was limiting during both data collection and when thinking about results in context. Restricting data collection to studies that used the UPDRS, resulted in a few credible studies being disregarded and some vague studies being accepted for analysis. Despite the comprehensiveness of the UPDRS, it cannot be the only measure that is considered when evaluating clinical effectiveness as it is a survey dependent on observations and patient reflection, meaning that without methodological standards UPDRS

scores could be influenced by any number of factors including time of day, conditions, how and by whom the questions are asked, etc.

4.3 Suggestions for Future Research

Although the limitations of this review present challenges, they also shed light on opportunities for future research. More Parkinson's Disease treatment specific comparisons that focus on clinical effectiveness are necessary, as without them Parkinson's Disease therapeutics developers cannot easily assess where areas for improvement lie, clinicians may not be able to recommend the treatment option best for a patient's particular symptoms, and patients are short changed information crucial to deciding which treatment is the best fit for them.

A second methodological suggestion for future research is using the UPDRS in its entirety. While the UPDRS has been referred to as the "gold standard" for assessing Parkinson's Disease symptoms, it has not been widely used in its entirety resulting in studies only assessing motor or cognitive symptoms, when in fact it may be more valuable to look at both [4,41].

A final suggestion for future research is to use the UPDRS as a complement to another, more objective outcome measurement. As outlined previously, without standards across observations and across studies on how the UPDRS is used, scores could be influenced creating a high potential for variability.

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