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A Prospective Study on Drug Utilization Pattern in Parkinson's Disease and Associated Comorbidities

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ABSTRACT

Introduction: Parkinson's disease is the second commonest neurodegenerative disease, affecting elderly population. This disease usually occurs due to deficiency of neurotransmitter dopamine in the corpus striatum following a lesion in substantia nigra and its projections. **Objective:** To assess the pattern of Antiparkinson's therapy and prevalence of comorbidities associated with Parkinson's disease. **Methodology:** This was a Prospective and Observational study performed on 106 Parkinson's Disease patients in Apollo Multi-Specialty hospital, Bengaluru. This study included inclusion and exclusion criteria, this study was assessed and evaluated by suitable statistical method. **Result:** Among the 106 patients included in the study majority (82) were males. Most of the patients (42) were in age group of 60-69 years. Hypertension (22.4%) was the most common comorbidity associated with Parkinson's Disease. The most frequently prescribed drugs for motor features were: levodopa+carbidopa (44.8%). The most common motor and non-motor symptoms were resting tremor (36.2%), rigidity (30.5%) and dementia (24.7%), psychosis (22.1%) respectively. For the management of motor and non-motor features, most of the prescription consisted of dual therapy (33.34%) and monotherapy (57.7%) respectively. The drugs used for Levodopa induced dyskinesia were levodopa+carbidopa (28.1%) combination followed by amantadine (25%). **Conclusion:** Patient with Parkinson's disease were characterized by high number of comorbidities, among them hypertension cover the highest percentage. Our study found that levodopa in combination with a peripheral decarboxylase inhibitor (44.8%) was most commonly used for the management of Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is the second commonest neurodegenerative disease, affecting elderly population. It is estimated that approximately 1 million persons in the United States, 1 million in western Europe, and 5 million worldwide suffer from this disorder. PD affects men and women of all races, all occupations, and all countries. The mean age of onset is about 60 years. The frequency of PD increases with aging, but cases can be seen in patients in their 20s and even younger. Based on the aging of the population and projected demographics, it is estimated that the prevalence of the disease will dramatically increase in the next several decades[1].

Pharmacologic treatment of Parkinson's disease can be divided into symptomatic and neuroprotective (disease modifying) therapy. Symptomatic anti-Parkinson disease medications usually provide good control of motor signs of Parkinson's disease for 4-6 years. After this, disability often progresses despite best medical management, and many patients develop long-term motor complications, including fluctuations and dyskinesias. Additional causes of disability in late disease include postural instability (balance difficulty) and dementia. Neuroprotective therapy aims to slow, block, or reverse disease progression; such therapies are defined as those that slow underlying loss of dopamine neurons. Currently, no proven neuroprotective therapies exist for Parkinson's disease. At the current time, the greatest interest in possible neuroprotection resides with the monoamine oxidase (MAO)-B inhibitors, selegiline, and rasagiline. Other agents of interest include creatine and isradipine. Clinical trials have not provided support for neuroprotective effects for vitamin E or coenzyme Q10[1].

Co-morbidity is defined as the occurrence of one or more chronic conditions in the same person with an index disease, occurs frequently among patients with Parkinson's disease.Hypertension(37.8%),Hyperlipidemia(21.2%),Diabetes(19.1%),Arthritis(16.82%) and CVS disorders(8.61%) are the major comorbidities associated with Parkinson's disease[2].

The study of prescribing pattern is a component of medical audit that does monitoring and evaluation of the prescribing practice of the prescribers as well as recommends necessary modifications to achieve rational and cost effective medical care and it helps to evaluate and suggest modifications in prescribing practices of medical practioners so as to make medical care rational.

Since there is an increase in the number of newly diagnosed Parkinson's disease over the past few years the amount of interest in the management of Parkinson's disease and its comorbidities has increased tremendously. In this study, we try to evaluate the detailed pharmacotherapeutical approaches to the management of Parkinson's disease and its comorbidities, which may help in better therapeutical outcome in the management of Parkinson's disease in future. The study also aims to find out prevalence of comorbidities associated with PD.

MATERIALS & METHODS

Study site:

The study was conducted in Apollo Multi Specialty Hospital and Research Center, Bengaluru.

Study design:

This was a prospective and observational study performed on 106 patients to assess the drug utilization pattern in Parkinson's Disease patients with their co-morbidities.

Study period:

The study was conducted over a period of 06 months starting from November 2018 to April 2019. **Ethical approval:** Ethical committee clearance was obtained by the Institutional Ethical Committee of Apollo Multi Specialty Hospital and Research Center.

Study procedure

1. **Patient Enrollment :**

A hospital based prospective study was conducted in Medicine and Neurology department of Apollo Multi Specialty Hospital and Research Center. The study was conducted on 106 patients who met the requirements of criteria. Patients who were not willing to give their consent, pregnant and lactating women were excluded from the study.

2. **Method of Data Collection :**

Pro-forma was used for data collection, which includes medication information (name, dose, frequency, route etc.) and patient information details (name, age, sex), socioeconomic

parameters, past medical history, disease diagnosed and duration of treatment. The antiparkinson's medications used in the Parkinsonism patients were recorded along with the other required laboratory details in a data collection form (Annexure) designed for the study. Data was evaluated using suitable statistical tools.

3. **Determination of drug utilization pattern:**

After the diagnosis was confirmed as Parkinson's disease, the entire relevant details were collected. Clinical data such as motor and non- motor features like rest tremor, rigidity, bradykinesia and dementia, psychosis were determined respectively. The prevalence of comorbidities associated with Parkinson's disease was evaluated based on patient medical history.

4. **Statistical Methods:**

Descriptive statistical analysis has been carried out in the present study. Chi-Square test has been used to find the significance of study parameters on categorical findings among different groups.

P value or significant considerations: Actual range (0.01<0.05<0.1)

*Strongly significant if P value is = 0.01.

*Moderately significant if P value is 0.01-0.05.

*Significant if P value is >0.05 to 0.1.

*Non-Significant if P value is >0.1.

Statistical Software:

The statistical software called SPSS (IBM) version 25 was used for the analysis.

Microsoft Word and Excel are used to generate tables and graph respectively.

RESULT AND DISCUSSION

Table No. 01. Below table represents the study sample distributed according to age group and gender:

Age Group	Gender		Total	Percentage
	Male	Female		
50-59 Years	12	2	14	13.2
60-69 Years	30	12	42	39.6
70-79 Years	25	5	30	28.3
80-89 Years	14	4	18	17.0
Above 90 Years	1	1	2	2.0
Total	**82**	**24**	**106**	**100.0**

Chi-square test=2.86 & p-value=0.58 (Not Significant)

As shown in table no:01, the age and gender distribution of the study population showed that 13.2% of patients belong to 50-59 years age group out of which 12 were males and 2 were females, 39.6% in 60-69 years age group out of which 30 were males and 2 were females, 28.3% in 70-79 years age group out of which 25 were males and 5 were females, 17% in 80-89 years age group out of which 14 were males and 4 were females and 2.0% of the total population were in >90 years age group out of which 1 was male and 1 was female. This implies the higher incidence of PD in males than female and treatment necessities are majorly required in age group of 60-69 years patients.

Table No. 02. Below table represents the study sample distributed according to co-morbidities

Co-Morbidities	No. of Patients	Percentage
Asthma	1	1.0
Bipolar Illness	3	3.1
Chronic Kidney Disease	2	2.0
Chronic obstructive pulmonary Disease	3	3.1
Depression/ Anxiety	7	7.1
Diabetes Mellitus	20	20.4
Hypertension	22	22.4
Hypothyroidism	10	10.2
Ischemic heart Disease	11	11.2
Multiple myeloma	1	1.0
Osteoarthritis	2	2.0
Pancytopenia	1	1.0
Seizure disorder	15	15.3
Total	**98**	**100.0**

According to the table, No- 02, the distribution of comorbid conditions among the study population showed that the most commonly found comorbidities in PD patients were HTN (22.4%), followed by DM (20.4%), seizure disorder (15.3%), IHD (11.2%), hypothyroidism (10.2%), depression/ anxiety (7.1%) and other diseases. Based on the result, it was found that patients with PD are highly associated with cardiovascular and endocrine disorders.

Table No. 03. Below table represents the study sample distributed according to motor features and gender:

Motor Features	Gender		Total	Percentage
	Male	Female		
Bradykinesia	15	6	21	20.0
Gait Disturbance/ Postural Instability	7	3	10	9.5
Hypophonia	1	1	2	1.9
Micrographia	2	0	2	1.9
Rest Tremor	28	10	38	36.2
Rigidity	29	3	32	30.5
Total	**82**	**23**	**105**	**100.0**

Chi-square test=5.782 & p-value=0.328 (Not Significant)

According to table No- 03, the common presenting motor symptoms during the study were resting tremor (36.2%), rigidity (30.5%) and bradykinesia (20.0%). The result also implies higher incidence of motor symptoms in males compared to females.

Table No. 04: Below table represents the study sample distributed according to non-motor features and gender:

Non-Motor Features	Gender		Total	Percentage
	Female	Male		
Anxiety	0	7	7	9.1
Bipolar Illness	1	2	3	3.9
Constipation	4	11	15	19.5
Delirium	0	1	1	1.3
Dementia	5	14	19	24.7
Depression	1	4	5	6.5
Genitourinal Disturbance	0	4	4	5.2
Insomnia	0	4	4	5.2
Psychosis	3	14	17	22.1
Sleep Disturbance	0	2	2	2.6
Total	**14**	**63**	**77**	**100.0**

Chi-square test=6.048 & p-value=0.735 (Not Significant)

According to table No- 04, the common presenting non-motor symptoms at the time of study were dementia (24.7%), psychosis (22.1%) and constipation (19.5%). The result also implies higher incidence of non-motor symptoms in males compared to females.

Table No. 05: Below table represents the study sample distributed according to prescription pattern of antiparkinson's drugs:

Antiparkinson's Drugs	No. of Patients	Percentage
Amantadine	13	7.6
Betahistine	1	0.6
Entacapone	7	4.1
Levodopa	18	10.5
Levodopa+Carbidopa	77	44.8
Levodopa CR	14	8.1
Levodopa+Carbidopa+ Entacapone	3	1.7
Pramipexole	7	4.1
Pramipexole ER	3	1.7
Rasagiline	5	2.9
Ropinirol	12	7.0
Trihexphenidyl	11	6.4
Total	**171**	**100**

As shown in table no:5, a total of 12 antiparkinson's drugs were prescribed to the study population. The drugs used in the management of PD were mainly dopamine precursor Levodopa in combination with a peripheral decarboxylase inhibitor Carbidopa, followed by Levodopa alone. In the current study majority (44.8%) of patients were prescribed with Levodopa+Carbidopa combination whereas 10.5% of patients were managed with Levodopa alone and 8.1% of patients were prescribed with Levodopa CR followed by amantadine (7.6%) and Ropinirole (7%) according to the patient needs and goals of treatment.

Table No. 06: Management of Levodopa induced Dyskinesia:

Complication	Prescribed Drug	No. of Patients	Percentage
Dyskinesia	Amantadine	8	25.0
	Entacapone	1	3.1
	Levodopa	1	3.1
	Levodopa+Carbidopa	9	28.1
	Levodopa CR	4	12.5
	Levodopa+carbidopa+entacapone	2	6.3
	Pramipexole	1	3.1
	Rasagiline	2	6.3
	Ropinirol	2	6.3
	Trihexyphenidyl	2	6.3
	Total	**32**	**100.0**

According to the table No- 06, The drugs used in the management of Levodopa induced dyskinesia were dopamine precursor Levodopa in combination with a peripheral decarboxylase inhibitor Carbidopa followed by amantadine. In the current study majority (28.1%) of patients were prescribed with Levodopa+Carbidopa combination along with Amantadine (25.0%) and Levodopa CR to manage dyskinesia.

Table No. 07: Distribution according to drugs prescribed for motor features:

Motor Features	Drug Prescribed	No. Of Patients	Percentage
Bradykinesia	Amantadine	4	2.33
	Levodopa	3	1.75
	Levodopa+Carbidopa	15	8.77
	Levodopa CR	1	0.58
	Pramipexole ER	1	0.58
	Rasagiline	1	0.58
	Ropinirol	4	2.33
	Trihexphenidyl	2	1.16
Gait Disturbance/ Postural Instability	Amantadine	2	1.16
	Betahistine	1	0.58
	Entacapone	1	0.58
	Levadopa	1	0.58
	Levodopa+Carbidopa	9	5.26
	Levodopa CR	1	0.58
	Ropinirol	1	0.58
Hypophonia	Levodopa+Carbidopa	1	0.58
	Pramipexole	1	0.58
	Rasagiline	1	0.58
	Ropinirol	1	0.58
	Trihexphenidyl	1	0.58
Micrographia	Levodopa+Carbidopa	2	1.16
	Rasagiline	1	0.58
Rest Tremor	Amantadine	3	1.75
	Entacapone	3	1.75
	Levodopa	7	4.09
	Levodopa+Carbidopa	32	18.71
	Levadopa CR	4	2.33
	Levodopa+Carbidopa+ Entacapone	1	0.58
	Pramipexole	4	2.33
	Pramipexole ER	1	0.58
	Rasagiline	1	0.58

	Ropinirol	4	2.3
	Trihexphenidyl	7	4.09
Rigidity	Amantadine	4	2.33
	Entacapone	3	1.75
	Levodopa	7	4.09
	Levodopa+Carbidopa	18	10.52
	Levadopa CR	9	5.26
	Levodopa+Carbidopa+ Entacapone	2	1.16
	Pramipexole	1	0.58
	Pramipexole ER	1	0.58
	Rasagiline	1	0.58
	Ropinirol	2	1.16
	Trihexphenidyl	1	0.58
	Total	**171**	**100**

According to table no.7, most commonly prescribed drugs for Bradykinesia were Levodopa+ carbidopa combination (8.77%) and amantadine (2.33%). For Gait Disturbance/Postural Instability Levodopa+carbidopa combination (5.26%) was prescribed. For Hypophonia Levodopa+carbidopa (0.58%) combination and Pramipexole (0.58%) were prescribed. For Micrograhia Levodopa+carbidopa combination (1.16%) and Rasagiline (0.58%) were prescribed. For Rest tremor, Levodopa+carbidopa (18.71%) and Trihexyphenidyl (4.9%) were prescribed. For Rigidity Levodopa+ carbidopa (10.52%) and Levodopa CR (5.26%) were prescribed. Based on result, it is found that most commonly prescribed drugs for all motor-features is Levodopa+ carbidopa.

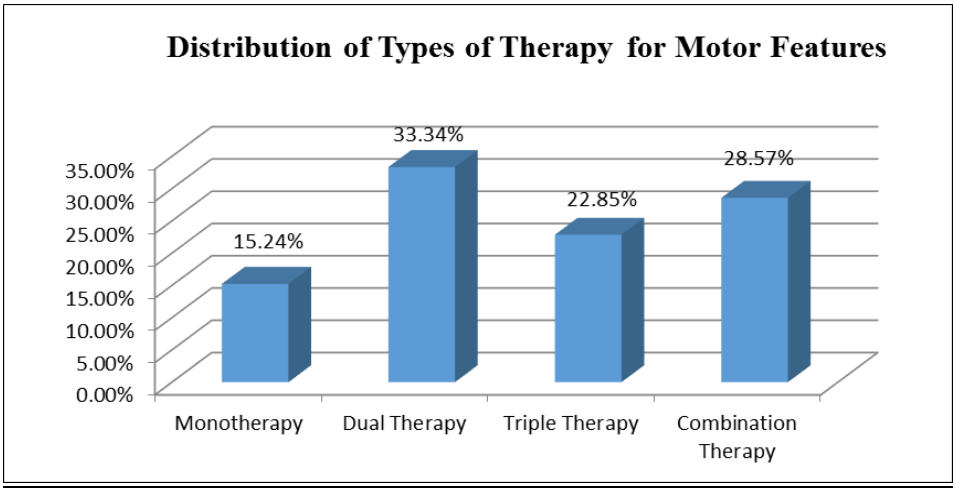

Figure No. 01: Below figure represents the study sample distributed according to type of therapy prescribed for motor features:

According to fig no.01, for the management of motor features, most of the prescription consisted of dual therapy (33.34%) and combination therapy (28.57%). Based on result, it was found that to treat motor features dual therapy and combination therapy is needed.

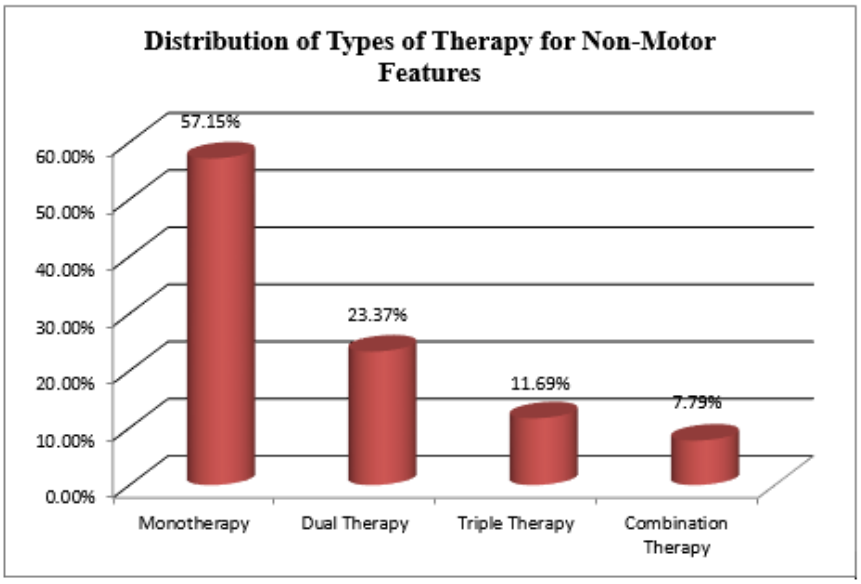

Figure No. 02: Below figure represents the study sample distributed according to type of therapy prescribed for non-motor features:

According to fig no. 02, in management of non-motor features, mostly monotherapy (57.7%) and dual therapy (23.37%) were used. Based on result, it was found that to treat non- motor features monotherapy was most commonly used.

DISCUSSION

Parkinson's disease (PD) is a worldwide progressive neurological disorder. Symptoms of Parkinson's disease begin to appear after 80% damage of these neurons. PD, at present, has no permanent cure, even there is variety of pharmacological and surgical treatment options available, usually end in severe disability. PD is not uncommon having a prevalence of 0.3% to 2% among 65 years and older persons. Table No. 01 represent that the highest numbers of patients diagnosed with PD were males constituting 77.4% of the total population included in the study and female patients constitute 22.6%. The possible cause for this may be the neuroprotective properties of female steroid hormones. A similar result was seen in a study conducted by **Miller IN *et al.*[3]** on Gender differences in Parkinson's disease: Clinical characteristics and cognition which showed that male preponderance of Parkinson's disease. Patients of various age group was enrolled for the current study among them the maximum

number of patients was seen in the age group of 60-69 years having 42 patients out of 106 total patients with a percentage of 39.6% compared to other age groups. According to table 02, the distribution of comorbid conditions among the patients showed that, the most commonly seen comorbidity in PD patients was Hypertension (22.4%), followed by Diabetes mellitus(20.4%), Seizure Disorder (15.3%) and Ischemic Heart disease(11.2%). Based on the result, it was found that the patients with PD are highly associated with hypertension due to damage in blood vessels in specific brain areas, such as basal ganglia, which contain the substantia nigra and the striatum. Similar findings were observed in a study conducted by **Hou L *et al.*[4]** which showed that hypertension was the most common comorbidity of PD. Table 03. Showed that the common presenting motor symptoms at the time of study were rest tremor (36.2%), rigidity (30.5%), and bradykinesia (20.0%). Our study found that the most presented motor symptoms is having a high prevalence in male patients than females. Similar findings was observed in a study conducted by **Hughes AJ *et al.*[5]** on the clinical features of Parkinson's disease in 100 histologically proven cases. According to table 04, the common presenting nonmotor symptoms during study were Dementia (24.7%), Psychosis (22.1%) and Constipation (19.5%). Similar finding were observed in a study conducted by **Liis Kadastik-Eerme *et al.*[6]** on Nonmotor features in Parkinson's disease: what are the most important factors. The result revealed that age, PD progression, presence of depression, dementia, lower quality of life, and higher doses or longer duration of levodopa treatment correlated significantly with the total burden of nonmotor symptoms. Table 05 represents that Levodopa-Carbidopa (44.8%) was the most commonly prescribed antiparkinson's agent. The majority of antiparkinsonian products dispensed were combination drugs containing levodopa with a decarboxylase inhibitor and some with a COMT-inhibitor as well which ultimately reflected that levodopa is considered the gold standard treatment of Parkinson's disease as similar to the study by **Singh *et al.*[7]** As per table 06, the most common drug or combination of drugs prescribed for dyskinesia were Levodopa-Carbidopa (28.1%), followed by Amantidine (25.0%). Using frequent smaller dosage of levodopa and fractionation is helpful to minimize peak dose dyskinesia. Similar result was observed in a study conducted by **Sanjay Pandey *et al.*[8]** on Levodopa-induced dyskinesia: clinical features, pathophysiology and medical management. Table no. 07 represents that motor features such as Bradykinesia, giat disturbance, micrographia, rest tremor and rigidity were mostly treated with Levodopa-Carbidopa combination exept hypophonia in which pramipexole, rasagiline, ropinirole, trihexyphenidyl and levodopa-carbidopa were equally prescribed. Similar findings were observed in a study conducted by **Gaida R *et al.*[9]** on prescription patterns for Parkinson's

disease in a South African patient population. The study implies that majority of the antiparkinsonian products prescribed (46.5%) were combination drugs containing levodopa with a decarboxylase inhibitor. Figure 01 revealed that 33.4% of the drugs prescribed for motor symptoms were dual therapy with Levodopa+Carbidopa, Ropinirol as the mostly dispensed drugs. Similar findings were observed in a study conducted by **Nabilia Dahodwala *et al.*[10]** showing that most of the patients were receiving dual therapy. According to Figure 02, 57.15% of the drugs prescribed for non-motor symptoms are monotherapy with zolpidem as mostly prescribed drug followed by dual therapy 23.37% and triple therapy 11.69%. similar findings were observed in a study conducted by **Monalisa Jena *et al.*[11]** on Antiparkinsonian drug utilization pattern and ADR Monitoring in a Tertiary Care Teaching Hospital: A hospital based observational study.

CONCLUSION

Based on the prescribing trends identified in this study, it can be seen that levodopa-carbidopa combination was still the preferred first line treatment for Parkinson's disease. The combination is best at controlling the symptoms of the condition, particularly slow movement and stiff, rigid body parts. Prescribing habits of drugs with therapeutic value predominated, mainly managed with levodopa-carbidopa and amantadine. It has been suggested that the anti-dyskinetic effects of amantadine are secondary to inhibition of NMDA receptors and using frequent smaller dosage of levodopa and fractionation is helpful to minimize peak dose dyskinesia.

Collectively, comorbidities have important implications in the health outcomes and clinical management of PD patients. In this study we found that hypertension, diabetes mellitus may appear before the onset of PD, thus highlighting the importance of recognizing these comorbidities as potential risk factors for PD.

The treatment approach chosen to treat the patient must be such that it should improve the patient quality of life. This study provided a basic knowledge about the prescribing pattern and also the comorbidities associated with PD patients. A vast study and analysis is required for extrapolating the results of our study with larger study population and longer duration of study period involving multiple follow up assessment to draw a concrete treatment strategy and also providing a safe drug and dosing schedule for patients receiving antiparkinson drugs.

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