Original Article

A Prospective Study of the Drug Prescribing Rate and Pattern and Assessment of Adverse Drug Reactions in Patients with Idiopathic Parkinson Disease in a Tertiary Care Hospital

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ABSTRACT

Aim: To determine the prescribing rate and pattern of antiparkinson drug use and to assess associated adverse drug reactions in patients with idiopathic Parkinson disease.
Materials and methods: Data was collected from the outpatients in neurology and medical records department. Patient demography, disease duration, symptoms, comorbid conditions, drug, dose, adverse drug reaction if any were noted. Information was collected again from the study participants during their routine follow up visit three months later to monitor the symptoms and adverse drug reactions (if any) occurring due to treatment. Causality assessment was done for the ADRs reported based on WHO scale.
Results: Male predominance was seen. A majority of patients were between 51 and 80 years and most of the patients had onset of disease between 51 and 70 years. The common presenting symptoms were rigidity, tremor and bradykinesia. Out of 100 patients, 48 received levodopa+carbidopa alone and the rest received combination therapy. The number of antiparkinson drug prescriptions increased with the disease duration. Sixty three patients had subjective improvement in the symptoms, of which bradykinesia was most common. Levodopa induced dyskinesia was the most common adverse drug reaction. The number of adverse drug reactions was significantly higher among patients receiving combination therapy.
Conclusion: Our study provides a basic knowledge about the drug prescribing pattern in the treatment of Parkinson disease and also the

adverse reactions to the drugs prescribed.
Keywords: Parkinson disease, adverse drug reactions, Levodopa, bradykinesia.

INTRODUCTION

Parkinson disease (PD) is one of the most common progressive neuro-degenerative disorders characterized by bradykinesia, rest tremor, muscle rigidity and postural instability. In India the incidence of Parkinson disease varies from 68 to 328.3 cases per 100,000 population.[1] Though it is defined as a movement disorder, PD can be accompanied by a variety of non-motor symptoms, which includes sensory, autonomic, cognitive, sleep and psychiatric disturbances. Almost all forms of parkinsonism are due to reduction of dopaminergic transmission within the basal ganglia.

About 75% of all cases of parkinsonism are idiopathic (Idiopathic Parkinson disease, IPD), while the remaining cases are rare secondary to neurodegenerative disorders, cerebro-vascular disease and drugs.[2] The diagnosis of Parkinson disease is based mainly on clinical examination, which includes the exclusion of other conditions and response to levodopa or a dopamine agonist.[3] It has a progressive course leading to functional disability which results in high medical costs. None of the available treatment strategies have disease modifying action. At present, pharmacological treatment is the mainstay for the management of Parkinson disease patients.[4] The commonly used medications for the treatment of Parkinson disease are levodopa/carbidopa, catechol-O-methyltransferase (COMT) inhibitors - entacapone and tolcapone, dopamine receptor (DA) agonists - bromocriptine, pramipexole and ropinirole, monoamine oxidase type B (MAO-B) inhibitors - selegiline and rasagiline, anticholinergics - trihexyphenidyl and NMDA receptor antagonist - amantadine.

The patient requires therapy with multiple drugs and for prolonged periods; the adverse effects of antiparkinson drugs and other co-morbid conditions often add on to the existing morbidity. Although, such adverse drug reactions are common, information about their incidence, severity and their impact on health is not available. A study assessing the adverse reactions for the drugs commonly used in movement disorders at a tertiary care hospital in India has been reported.[5] There are few published pharmacoepidemiological studies on drug usage patterns in Parkinson disease.[4, 6] Hence, we decided to undertake this study of drug prescribing pattern and adverse reactions in patients with Parkinson disease in a tertiary care hospital.

MATERIALS AND METHODS

The study was carried out after obtaining approval from Institutional Ethics committee (IEC 348/2011), Kasturba Hospital, Manipal. This was a prospective, observational study conducted in department of Neurology and medical records department (MRD), Kasturba Hospital, Manipal from December 2011 to August 2013.

Inclusion criteria

Outpatients of either sex with idiopathic Parkinson disease.

Exclusion criteria

Patients with parkinsonism due to other causes.

Patients with other movement disorders

After obtaining informed consent from the patients attending Neurology outpatient department, the data regarding age, gender, detailed medical history, age of onset of disease and its duration, clinical signs and symptoms, drugs prescribed for Parkinson disease and other concomitant medications, comorbid conditions and adverse drug reactions were collected by interacting with the patient and from patient's case record. Information was collected again from the study participants during their routine follow up visit three months later to monitor the symptoms and adverse drug reaction (if any) occurring due to treatment. The patient's subjective response of relief or no relief of symptoms during the follow up visits was recorded. Adverse reactions (ADRs) to antiparkinson drugs and concomitant drugs, if any were noted. Causality assessment was done for them based on WHO scale for the causality assessment of suspected ADR[7].

STATISTICAL ANALYSIS

A descriptive approach was used for data analysis. Data was analysed for statistical significance using Chi-Square test for categorical data and Independent sample t-test for numerical continuous data. The results were expressed as percentage. A p-value<0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

One hundred patients diagnosed with idiopathic Parkinson disease were included in the study during the study period. All were old cases of idiopathic Parkinson disease already receiving treatment. Among 100 patients who were diagnosed to have IPD, 67 (67%) were males and 33 (33%) were females. There was a higher male predominance in our study group with male to female ratio of 2.03: 1. The current age of the patients varied from 41 to 85 years. A majority (81%) of patients were between 51-80 years of age with the mean current age being 64±10.1 years. About 63% patients were in the age group 51-70 years at the onset of disease. The mean age at the onset of disease was 60.9±9.7 years. There was no statistically significant difference in the mean age of onset of the disease between males and females. The mean duration of disease was 3.09±2.28 years. The common presenting symptoms at the time of enrolment into study were rigidity (94%), tremor (93%) and bradykinesia (93%) [Figure1].

The total number of prescriptions was 344. All patients were on antiparkinson drugs, which accounted for 176 prescriptions (mean ± SD: 1.76±0.87/patient).

In 97 patients, treatment was initiated with combination of levodopa with carbidopa while in 3 patients treatment was initiated with seligiline. But at the time of enrolment into study all patients with IPD were on levodopa – carbidopa combination. Prescription rates of other drugs are given in Figure 2. The mean total daily dose of levodopa at the time of enrolment into study was 307.5±136.9 mg.

Out of 100 patients, 48 received combination of levodopa with carbidopa only. The total number of antiparkinson drugs prescribed was 176 (mean ± SD: 1.76±0.87/patient). There was no statistically significant difference in the current age (p=0.35) and age at onset of disease (p=0.88) among the individuals who received monotherapy or combination therapy. Patients on monotherapy had a mean duration of disease of 2.3±2.0 years while those on combination therapy had a mean duration of disease of 3.7±2.3 years. The number of APD prescriptions increased with the disease duration which was statistically significant (p=0.02) (Table 1).

Seventy eight patients had co-morbid conditions. The common co-morbid illnesses were hypertension (30%), diabetes mellitus (24%). Concomitant medications are given in Figure 3.

Follow up

Out of 100 patients enrolled in the study, 88 patients came for subsequent follow up visit during the study period. Sixty three patients (72%) had subjective improvement in the symptoms. There was no change in symptoms in 23 patients (26%) whereas two patients complained of worsening of symptoms. Twelve patients did not come for follow up visit. Out of 63 patients who reported improvement in symptoms, 54 patients (85.71%) had improvement in bradykinesia and rigidity; 48 patients (76.19%) had improvement in tremor. About 34 (53.96%) out of 63 patients who reported improvement in symptoms, were on levodopa+carbidopa alone, 24 patients (38.09%) were receiving dual therapy and five patients (7.93%) on triple therapy. There was no statistically significant difference in improvement of symptoms between patients receiving monotherapy and combination therapy (p=0.14). [Figure 4]

Among 23 patients who had no improvement in the symptoms, the dose of levodopa was increased in 17 patients and dopamine agonist was added in remaining six patients. Trihexyphenidyl was added to the regimen in two patients who reported worsening of tremors. Five out of 88 patients had new symptoms at follow up visit. Three patients complained of weakness and remaining two had constipation. All five patients were reassured and laxatives were given to patients with constipation

Out of 88 patients who came for follow up, twenty seven patients reported adverse drug reactions, of which dyskinesia due to levodopa was reported by 26 patients. The dose of levodopa was reduced and frequency of administration was increased in 10 of these patients; while in seven patients dose of levodopa was reduced and a sustained release formulation of levodopa was added. In the remaining six patients, amantadine was added and the dose of levodopa was reduced. The other ADR was trihexyphenidyl induced dry mouth in one patient; the patient was reassured.

According to WHO scale for the causality assessment of suspected adverse drug reaction, all were classified as "possible." There was no statistically significant difference in the number of ADRs between males and females (p=0.47). The number of ADRs was significantly higher among patients receiving combination therapy as compared to monotherapy (p<0.001) [Table 2].

DISCUSSION

The treatment of Parkinson disease is complex which involves the use of multiple drugs both for Parkinson disease and other concomitant illnesses. Most of the studies conducted in the past have concentrated on the estimation of prevalence of Parkinson disease.[8-10]This study was undertaken to evaluate drug prescribing pattern and assessment of adverse drug reactions in patients with idiopathic Parkinson disease in a tertiary care hospital.

In our study, male predominance was seen. The male to female ratio being 2.03:1. This was in concordance with study conducted by Van Den Eeden et al.[1] Most prevalence studies that indicated higher prevalence of Parkinson disease in men or in women, were based on medical records, whereas most surveys with a personal screening for disease found no significant sex differences. These findings suggest that the risk of Parkinson disease is equal in men and

women, but the referral to medical services varies by sex across populations.[11]

All patients received one or more antiparkinson drugs. Levodopa combined with carbidopa was given to all the patients, as at present levodopa remains the most effective symptomatic treatment for Parkinson disease and the gold standard against which new therapies are compared.[2] A similar finding was reported in the study conducted by Leoni et al.[4] Other commonly prescribed antiparkinson drugs were anticholinergic agents followed by dopamine agonist, MAO-B inhibitor, NMDA antagonist and COMT inhibitor.

There is no single treatment approach that is universally accepted to treat Parkinson disease; management of Parkinson disease should be tailored to the needs of the individual patient. Inspite of treatment, the disease progresses and eventually patients require multiple drugs.[2,12] In our study, it was observed that patients with longer duration of disease were on combination of drugs as compared with those receiving monotherapy suggesting a strong relation between disease duration and the number of antiparkinson drugs prescribed for the disease. This finding was also seen in the study conducted by Leoni et al.[4] The number of antiparkinson drugs prescribed was not associated with the current age and age at onset of disease. In contrast, in another study[4] the number of APD prescriptions per patient showed an inverse correlation with both current age and age of the patient at IPD onset.

A majority of the patients who visited the hospital were already diagnosed and referred from other centers. From the past treatment history, all the patients were started with monotherapy and later on, there was addition of other drugs or change in the drugs depending on the response to the treatment and course of the disease. Over the course of treatment, the effect of levodopa wears off or becomes inconsistent leading to motor fluctuations and abnormal involuntary movements.[4] Anticholinergics are given as adjuvant in the tremor predominant patients. Dopamine agonist, COMT inhibitors and MAO-B inhibitors are added to levodopa-carbidopa regimen in patients who developed end dose wearing off.[12] In our study, dopamine agonist or COMT inhibitors were added in patients who developed end dose wearing off whereas anticholinergic drug was added in tremor predominant patients.

The most common indication for non-antiparkinson drug use was hypertension which affected almost one out of three patients. Hypertension is common in elderly patients, so it is not surprising that in our study sample it is the most common comorbid illness. The study conducted by Semchuk *et al* did not show any association between hypertension and Parkinson disease.[13]

Though majority of patients had bradykinesia, tremors and rigidity at the time of enrolment into our study, the severity was less compared to initiation of therapy. During follow up visit, more than two-third of the patients had subjective improvement in the symptoms. Among them, the most commonly improved symptoms were bradykinesia followed by rigidity and tremor. In our study, there was no difference in improvement of symptoms in patients receiving combination therapy as compared to those on monotherapy. Similar results were seen in clinical trials.[14,15]

Twenty seven patients reported ADRs in our study. The number reported being less as compared with the incidence of ADRs as most of the ADRs goes unreported.[16] It could also be on account of the patients being followed up only once after enrolment in the study and the shorter mean duration of the disease in our study population. Dyskinesia is one of the most common adverse effects due to levodopa.[17] Indyskinesias, use of lower doses of levodopa is often beneficial. With the lowering of the levodopa dose,

dyskinesias improve but at the cost of returning parkinsonian features; this results in an increase in dosage frequency or addition of another agent like amantadine to counteract the effects of using a lower levodopa dose.[12] In our study, levodopa induced dyskinesia was the most common ADR which was treated by reducing the levodopa dose along with increasing the frequency of levodopa administration or addition of sustained release formulation of levodopa or by addition of amantadine.

There are some limitations in our study. Improvement in symptoms was assessed by patient's subjective response of relief or no relief of symptoms. UPDRS (Unified Parkinson Disease Rating Scale), commonly used to assess the course of disease and improvement of symptoms, was not used in the hospital. Also, patients were followed up for a short period.

CONCLUSION

At present, there are only a few studies on drug prescription pattern, adverse drug reactions and epidemiology of Parkinson disease in India. Our study provides a basic knowledge about the drug prescribing pattern in the treatment of Parkinson disease and also the adverse reactions to the drugs prescribed. Before extrapolating the results of our study to general population, further extensive studies are required with larger study population and longer duration of study period involving multiple follow up assessment to draw a concrete treatment plan and also to promote the safety of patients receiving antiparkinson drugs.

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Table 1. Relation between the type of antiparkinson drug treatment and disease duration

APD treatment	Number of patients	Duration of disease in years (mean ± SD)
MONOTHERAPY (Levodopa+carbidopa)	48	2.3±2.0
COMBINATION THERAPY (Levodopa+carbidopa+other APDs)	52	3.7±2.3*
Dual drug therapy	32	2.9±2.0
Triple drug therapy	17	4.9±2.4
Four drug therapy	2	5.0±1.4
Five drug therapy	1	5

*p=0.02 (Independent sample t-test)

Table 2. Adverse drug reactions with respect to type of therapy

ADR	Number of patients receiving Monotherapy	Number of patients receiving Combination therapy
Present	3	24*
Absent	36	25

*p<0.001 (Chi-Square test)

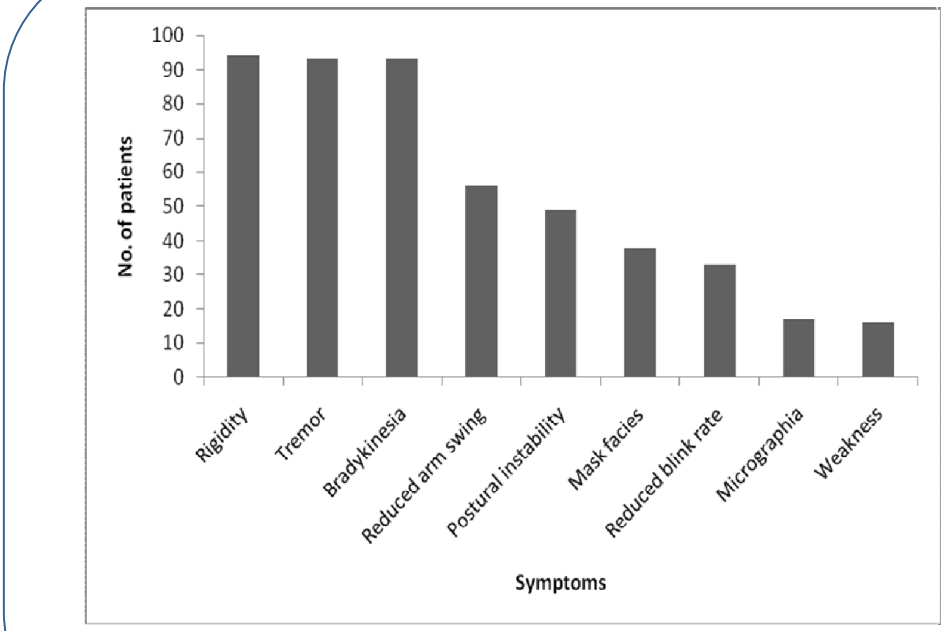

Figure 1. Initial symptoms

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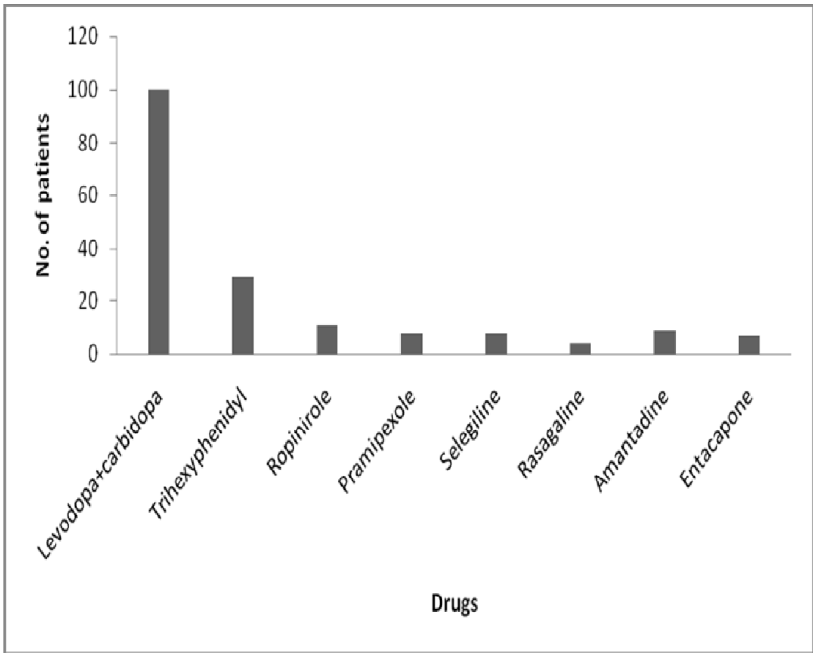

Figure 2. Prescription rate of different antiparkinson drugs

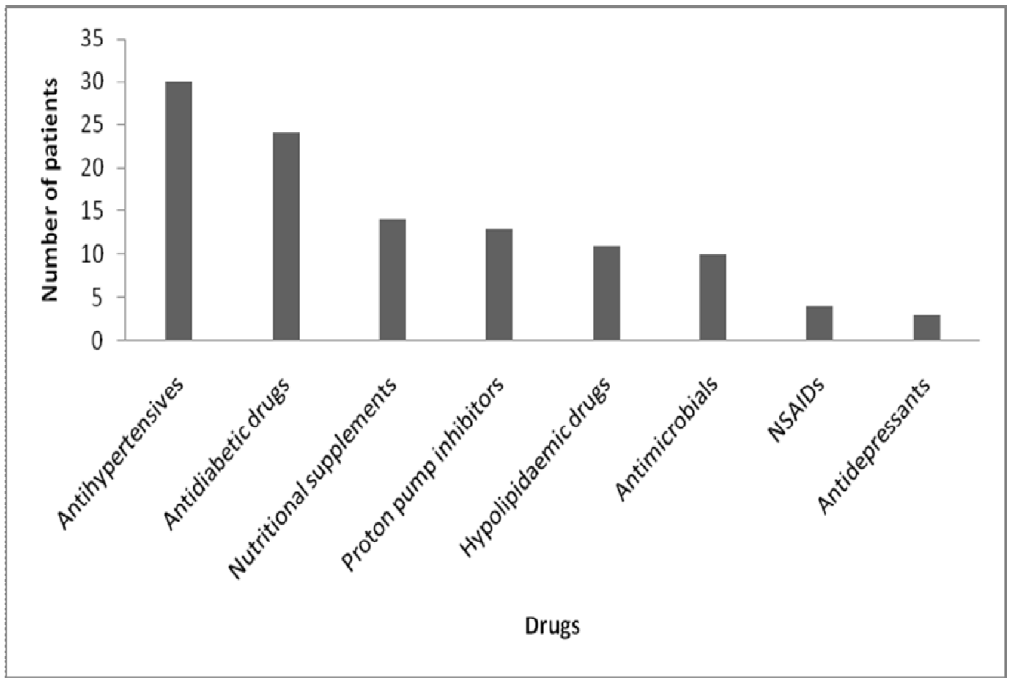

Figure 3. Frequency of concomitant drugs prescribed

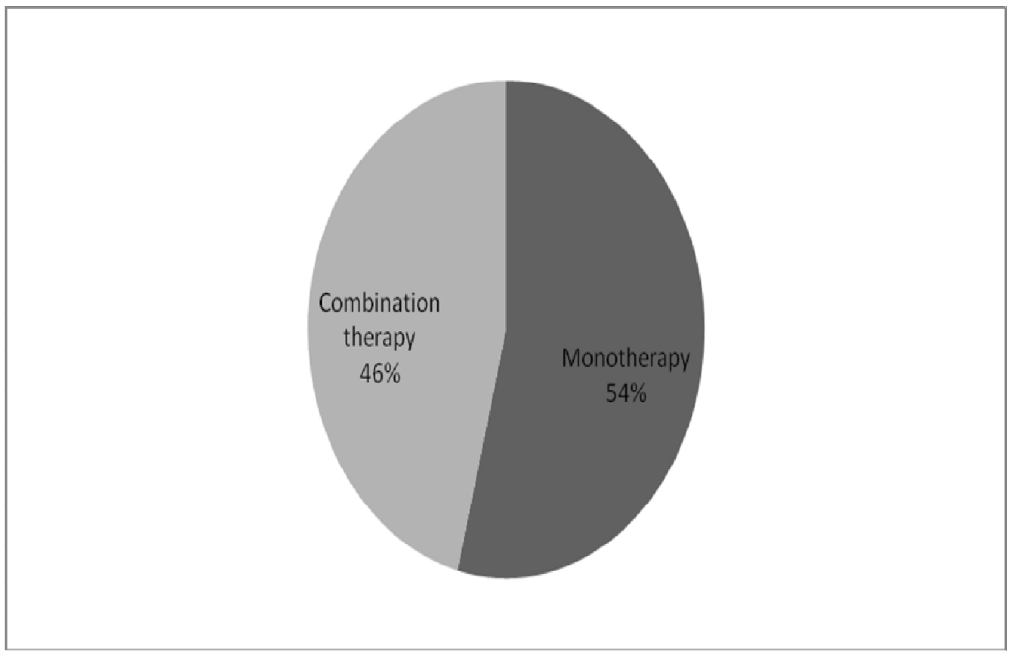

Figure 4. Improvement of symptoms in patients receiving monotherapy and combination therapy (n=63)