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Research Article

Antiparkinsonian Drug Utilization Pattern and ADR Monitoring In a Tertiary Care Teaching Hospital: A Hospital Based Observational Study

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ABSTRACT

Introduction: Parkinson's disease (PD) is chronic progressive neurodegenerative disorder represented by tetrad of symptoms such as bradykinesia, tremor, rigidity and gait disturbances. It results from the degeneration of dopamine-generating cells in the substantia nigra in midbrain. This study was done to determine the prescribing pattern of antiparkinsonian drugs and associated adverse drug reactions in patients.

Materials & methods: Data was collected from the case sheets in retrospective manner from Department of neurology of IMS & SUM Hospital, Bhubaneswar, India. The demographic profile, disease duration, symptoms, categories of drug, adverse drug reaction if any were noted and analyzed.

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 80 years. The common presenting symptoms were rigidity, tremor and bradykinesia. The commonest category of drug prescribed was levodopa either as monotherapy or in combination with other agents. 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: This study enlightens our knowledge regarding the utilization profile of antiparkinsonian drugs and related adverse drug reactions.

Key-words: Parkinson disease, adverse drug reactions, Levodopa, Bradykinesia, Dopamine.

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INTRODUCTION:

Parkinson's disease (PD) is a worldwide progressive neurological disorder that occurs due to neuronal damage or impairment which produces dopamine in a midbrain structure & responsible for controlling muscle movement specifically coordinated muscle function. 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 [1-3], usually end in severe disability. As it is a chronic disease, the disease burden increases with loss of quality of life which may be due to both disease and drug associated risks, requiring extensive utilization of both health care and community services [4-8].

PD is not uncommon having a prevalence of 0.3% to 2% among 65 years and older persons [9].There is various development of advances in pharmacological management of PD in recent years which ranges from levodopa as the only effective treatment in the early 1960s[10],to other compounds such as enzyme inhibitors and dopamine agonists. Pharmacoepidemiological data also showed that the traditional patterns of prescribing in different countries even in different tertiary care hospitals are different from each other [11].

Economic status of a country (health care cost) [12] is having a greater effect over a predicted increase in life expectancy [13] of elderly patients with PD. As the prevalence of PD rises, the burden on economic status of the family members increases. Therefore physician should maintain good prescribing habit to decrease the health care cost[14]. There is also lack of knowledge about the difference of prescribing pattern in different organization or tertiary care hospitals which is specifically influenced by lifelong burden of a disease which is in tern affected by many factors.

AIM OF THE STUDY:

The present study aimed to evaluate the prescribing pattern of antiparkinsonian drugs including the demographic profile, clinical pattern, the categories of drug, patterns & types of prescription and their adverse effects.

PATIENTS & METHODS:

The study was a retrospective hospital based prescribing pattern review conducted in the Neurology department in collaboration with the Department of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, Odisha. Permission from the institutional ethics committee was obtained. The duration of study was one year from Jan 2014 to Jan 2015. Medical case sheets, drug charts, laboratory investigations and neuro imaging were recorded in a self-designed standardized proforma and analyzed. The collected data included the following elements: demography, current diagnosis, medical history, medications prescribed {dose, route of administration, frequency, therapy duration, indication, pharmacological classification, marketing categories [generic or branded, single or fixed dose combination and new or old drugs per Central Drug Standard Control Organization (CDSCO) - India classification]} and ADRs occurred to the sample population.

Only patients aged 40 years and older were included in this study as PD is more common in patients of this age group (Movement Disorder Society Task Force on Rating Scales for Parkinson's Disease, 2003)[15]. The data contained information about patients receiving antiparkinsonian medication on a chronic basis.

Diagnosis of PD was defined as presence of the ICD-10 code for ''Parkinson's disease'' (G-20). Prescription of anti-Parkinson drugs was defined as presence of the ATC code for ''anti-Parkinson drugs'' (N04A). Patients younger than 30 years were excluded because they likely suffered from antipsychotic-induced parkinsonism, given that the mean age of PD onset is 62.7 years and 90.2% of PD patients are 40 years or older in the nationwide registry[16]. Exclusion criteria were adjusted as appropriate for the analytical purpose.

OBSERVATIONS & RESULTS:

Parameters for evaluation:

The parameters analyzed for our study were demographic profile of the study population(gender, age), PD duration, prescribed anti-Parkinson drugs, first-line drug, other drug data's (group of the drug, name of the drug,

mono or polytherapy, number of drugs per prescription, formulation) and associated adverse drug reactions with the prescribed group of drugs.

A total of 462 patients were prescribed nine types of antiparkinsonian products, with 148(32.1%) of the patients being females and 314(67.9%) being males (Table 1). This gives a male to female ratio of 2.12:1. The average age of the patient population was 59.3±8.5 years. The reason for the decline in the number of patients beyond the age of 70 years could be due to mortality or low life expectancy in developing countries like India. The age of our study population varied from 41 to 93 years. A majority (97.9%) of patients were between 51-80 years of age. 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 56.3±9.2 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 3.92±3.28 years.

Table 1: Demographic profile analysis of the study population diagnosed with Parkinson's disease: n= 462 [m-314, f - 148(2.12:1)]

Age in years	**Male with % 314(67.9)**	**Female with % 148(32.1)**
40-49	3(0.95)	1(0.67)
50 – 59	133(42.3)	68(45.9)
60 – 69	101(32.1)	46(31.08)
70 – 79	52((16.5)	23(15.5)
80 – 89	21(6.68)	8(5.4)
≥ 90	4(1.2)	2(1.3)

The common presenting symptoms at the time of enrolment into study were tremor, bradykinesia, and rigidity. (Table 2)Duration or chronicity of PD was calculated from the month from official diagnosis until the last month of recorded treatment of PD.

Table-2 Clinical Features of Parkinson`s disease (n=462)

Clinical Features	**Number of patients (%)**
Rest tremor	431(93.2)
Bradykinesia	416(90.04)
Rigidity	403(87.2)
Gait disturbances/ Postural instability	226(48.9)
Micrographia	114(24.6
Masked facies(Hypomimia)	258(55.8)
Reduced Eye blink	180(38.9)
Soft voice(Hypophonia)	149(32.2)
Dysphagia	88(19.04)
Freezing	45(9.7)
Anosmia	52(11.2)
Sensory disturbances(e.g.-pain)	114(24.6)
Mood disorder(e.g.-Depression)	92(19.9)
Sleep disturbances	62(13.4)
Autonomic disturbances (orthostatic hypotension, gastrointestinal disturbances, genitourinary disturbances, sexual dysfunction)	118(25.5)
Cognitive impairment/ Dementia	42(9.09)

Total Number of antiparkinsonian drugs prescribed to the study population was 2414. (Table 3) Number of antiparkinsonian drugs per prescription was 2.17. The drugs used in the management of PD were mainly dopamine precursors Levodopa alone and in combination with peripheral decarboxylase inhibitors (carbidopa). Independent of the antiparkinsonian drugs use profile (either monotherapy or combination therapy, Levodopa 1291(53.4%) was the most frequently prescribed category followed by Trihexyphenidyl 384(15.9%) and Amantadine 148(6.13%) (Table 2). The most frequently used combination therapy consisted of Levodopa + Dopa -

decarboxlyase inhibitor 1291(53.4%) followed by Levodopa + COMT inhibitors 66(2.73%) of the prescribed drugs are from the Essential drug list (EDL). The second most common categories of drugs were the central anticholinergic agents, 384(15.9%) followed by dopamine agonists which included pramipexole and ropinirole 281 (11.6%).

Table 3: Categories of antiparkinsonian drugs prescribed in our set up: (n=2414)

Name of the drugs	No of prescriptions with percentages
Drugs acting on brain dopaminergic system	
Levodopa + Dopa -decarboxlyase inhibitor	1291(53.4)
Non ergot alkaloids: Pramipexole	134(5.5)
Non ergot alkaloid: Ropinirole	147(6.08)
Selective MAO B inhibitors: Selegiline	89(3.68)
Selective MAO B inhibitors: Rasagiline	108(4.47)
COMT inhibitors: Entacapone	47((1.94)
Levodopa + COMT inhibitors	66(2.73)
Glutamate (NMDA receptor) antagonist or Dopamine facilitator): Amantadine	148(6.13)
Drugs acting on brain cholinergic system	
Central anticholinergics: Trihexyphenidyl, Procyclidine	384(15.9)

A total number of 2414 drugs (Table 4) were prescribed in 1108 prescriptions (number of prescriptions are more as compared to the total number of cases as the patients comes for follow up for number of times & drugs were changed or new drugs were added) and the average number of drugs per prescription was found to be 2.17. The number of fixed dose combination drugs prescribed was 1528.

Table 4: Analysis of prescriptions

Number of prescriptions	1108
Total no. of drugs prescribed	2414
Total no. of drugs prescribed through oral route	2414
Average no. of drugs prescribed per prescription	2.17
Number of fixed dose combinations	1357

Polypharmacy was seen in 996(89.9%) prescriptions as compared to 112(10.1%) prescriptions with monotherapy. (Table 5) Most of the polytherapy prescriptions consisted of triple therapy. Only 66 patients were administered with 4 drug therapy and even very less with five drug therapy i,e 18 patients.

Table 5: Type of prescription

Type of prescription	No. of prescription (%)1108
Monotherapy	112(10.1%)
Polytherapy	996(89.9%)
• Dual drug therapy • Triple drug therapy • Four drug therapy • Five drug therapy	• 257(23.1) • 655(59.1) • 66(5.9) • 18(1.6)

In our study group 103 patients developed 144 ADRs of various types. (Table 6).Some patients developed more than one ADR (11 patients developed 2 ADRs and 4 patients developed 3 ADRs). In most of the ADRs, the organ system affected was central nervous system & gastrointestinal system. The most common drug or

combination of drugs implicated for ADRs were Levodopa + Dopa -decarboxlyase inhibitor (Carbidopa) (50.69%) followed by pramipexole, ropinirole (22.9%) and Central anticholinergics (14.58%).

Table 6: Spectrum of suspected ADRs noted: n =144 ADRs in 103 patients

Name of the drugs	No (% of all ADRs, n=144(31.1%)	Side effects
Levodopa + Dopa - decarboxlyase inhibitor (Carbidopa)	73(50.69)	Nausea, vomiting, orthostatic hypotension, wearing off effect, dose related dyskinesia, dopamine dysregulation syndrome, impulse control disorders
Non ergot alkaloids: Pramipexole, Ropinirole	33(22.9)	Nausea, vomiting, constipation, dizziness, fatigue , somnolence (sleepiness), dry mouth, muscle spasms, peripheral edema, dyskinesia, orthostatic hypotension, hallucination, cognitive impairment, sedation, impulse control disorders
Selective MAO B inhibitors: Selegiline, Rasagiline	3(2.08)	Increased dyskinesia, postural hypotension, dizziness, nausea, headache, insomnia, stomatitis, dyspepsia headaches, joint pain
COMT inhibitors: Entacapone	2(1.3)	Nausea, vomiting, orthostatic hypotension, increased dyskinesia, diarrhea, abdominal pain, back pain, constipation
Levodopa + COMT inhibitors(Entacapone)	3(2.08)	Nausea, vomiting, wearing off effect, dose related dyskinesia
Glutamate (NMDA receptor) antagonist or Dopamine facilitator): Amantadine	9(6.25)	Livido reticularis, weight gain, dry mouth, constipation, ankle swelling, cognitive dysfunction, dizziness, hallucinations.
Central anticholinergics: Trihexyphenidyl, Procyclidine	21(14.5)	Cognitive impairment, confusion, hallucinations, urinary dysfunction, dryness of mouth, nausea, blurred vision, nervousness

DISCUSSIONS:

Many studies have shown that Parkinson's disease is more common in men than women [17, 18] which corroborates with our study showing 148(32.1%) and 314(67.9%) males suffered from PD with a male to female ratio of 2.12:1. But our study differs from two Japanese studies which have shown a female prevalence in PD [19, 20] . Another study conducted in France showed no significant difference between males and females [21]. The possible cause for this may be the neuroprotective properties of female steroid hormones, or alternatively gender differences in exposure to environmental and occupational risk factors or gender-specific genetic influences [22, 23]. It has been previously well described that gender differences in the risk of developing PD & concluded that higher incidence rates in males, particularly in the oldest age groups [23].

The common presenting symptom during our study period was tremor, bradykinesia, and rigidity similar to other studies [24, 25, 26]. However, 25 % of patients with PD never develop tremor. [24] Resting tremors in PD is usually a supination-pronation tremor, asymmetric, and most prominent in the distal part of an extremity, lost during sleep, reduced in action, and worsened by excitement, anxiety, or apprehension. Bradykinesia, referring to slowness of movements with difficulties in initiating and maintaining motions, and rigidity, characterized by increased resistance to passive stretch of skeletal muscles, are less common than rest tremor but are still frequently seen at onset of PD.

In this study, we examined trends of anti-Parkinson drugs prescribed to PD patients from January 2014 to 2015 in our hospital, and found that L-dopa was the most frequently used and was prescribed to more than half of

the patients during the study period which is similar to various other studies [27].]While the introduction of new non-ergot agents may have reduced the prescription of ergot agents, it had little influence on the prescription of L-dopa. 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 and similar to the study by Singh *et al.,* 2007& Stern, 2001 [28, 29]. In general practice, neurologists are not keen to prescribe anticholinergics for the treatment of PD as first-line treatment modalities due to their limited efficacy and neuropsychiatric side effects [30, 31, 32] similar to our study (Central anticholinergics; 14.58%).But in some studies it was seen that, anticholinergics were prescribed around 30% of new PD patients as first line therapy, and were used in approximately 30% of all PD patients in this study [27]. The second most dispensed group of drugs were the anticholinergic agents (15.9%), Trihexiphenydyl, Procyclidine followed by dopamine agonists (11.58%)which included pramipexole and ropinirole of the total number of antiparkinsonian products dispensed dissimilar to the study of Gaida *et al* 2014 [33] which depict that second most prescribes group of drugs were dopamine agonists 39.80% followed by anticholinergic agents 9.20% .[33] The MAO-B inhibitor selegiline & rasagiline (8.15%) and the anti-viral agent amantadine only made up 6.13% similar to the study of Gaida *et al* 2014 [33]. Bromocriptine is not the choice of dopamine agonist as there is plenty availability of pramipexole and ropinirole. A guideline for the treatment of Parkinson's disease published by the Scottish Intercollegiate Guidelines Network (2010) does not recommend the use of ergot derived dopamine agonists such as bromocriptine for the first line treatment of Parkinson's disease due to the risk of developing moderate to severe cardiac valvulopathy [34].

Polypharmacy was commoner (89.9%) as compared to monotherapy (10.1%) in our study population which corroborates with other studies [35]. Due to long chronic course of levodopa administration, the effect of levodopa wears off leading to fluctuations in the motor activities and abnormal involuntary movements like dyskinesia similar to various previous studies for which anticholinergics are added as adjuvant [36]. Dopamine agonist, COMT inhibitors and MAO-B inhibitors were also added to levodopa carbidopa regimen in patients who developed these phenomena [37]. In our study, dopamine agonist or COMT inhibitors were added in patients who developed end dose wearing off.

103 patients reported 144 ADRs in our study which was less as compared to other studies due to lack of awareness of self reporting of ADRs [38]. According to WHO scale for the causality assessment of suspected adverse drug reaction, all were classified as "possible." The number of ADRs was significantly higher among patients receiving combination therapy as compared to monotherapy. Dyskinesia & other motor disturbances were the most common adverse effects due to levodopa similar to other studies [39]; Levodopa preparations lead in the long term to the development of motor complications characterized by involuntary movements called dyskinesias and fluctuations in the response to medication [40]. When this occurs, PD patients change rapidly from stages with good response to medication and few symptoms ("on" state) to phases with no response to medication and important motor symptoms ("off" state). [40] For this reason, levodopa doses are kept as low as possible while maintaining functionality. Incidence of dyskinesia decreased with decreasing the dose of levodopa and addition of another agent [41].

Dopamine agonists produce significant, although mild, side effects including somnolence, hallucinations, insomnia, nausea, and constipation [40]. Sudden onset of sedation & sleep was reported with pramipexole similar to previous studies may be due to dysregulating dopaminergic input to the brain's reticular activating system, which controls sleep and arousal [42].Dyskinesias with dopamine agonists are rare in younger patients, but along other side effects, more common in older patients [43]. MAO-B inhibitors improve motor symptoms and delay the need of taking levodopa when used as monotherapy in the first stages of the disease, but produce more adverse effects and are less effective than levodopa.

CONCLUSION:

A very few studies have been published regarding the epidemiology, utilization pattern and adverse drug reaction monitoring of drugs used in the management of Parkinson's disease in India. This study provides a basic knowledge about the drug prescribing pattern and also the adverse reactions to the drugs prescribed for PD. 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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