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Original Article

Pharmacology Section

Treatment Reconciliation in Parkinson's Disease Patients with Particular Reference to Wearing-off and Motor fluctuations: A Registry-based, Prospective, Observational Study

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ABSTRACT

Introduction: Parkinson's Disease (PD) is the second most frequent neurodegenerative disease and dopaminergic agents are frequently used as a treatment while 'end of dose deterioration' or 'Wearing-Off (WO)' phenomenon is common with these agents. Treatment reconciliation may be helpful in this situation and there is dearth of studies especially in India.

Aim: To study the WO effects in patients of PD, their pharmacotherapy and outcome.

Materials and Methods: This registry-based, prospective, observational, outcomes-based study was conducted in the Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India, in collaboration with Department of Neuromedicine of Kolkata Medical College and private clinics of a Neurologist from January 2020 to December 2021. An attempt was also undertaken to make a registry of Idiopathic Parkinson's Disease (IPD) patients. WO Questionnaire 19-items (WOQ-19), Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS Scale), The 39-items Parkinson's Disease Questionnaire (PDQ-39 questionnaire), The 8-items Morisky Medication Adherence Scale (MMAS scale), suspected Adverse Drug Reaction (ADR) Reporting Form of Indian Pharmacoepia commission (version 1.3), World Health Organisation- Uppsala Monitoring Centre (WHO-UMC) Scale, Naranjo causality assessment scale, Hartwig and Seigel's Severity Assessment Scale were used in the present study. The study was commenced after obtaining approval from institutional ethics committee. The data was then analysed with parametric or non parametric tests using (mean±Standard Deviation (SD), median, Fisher's-exact test, Friedman's Analysis of Variance (ANOVA) test, Wilcoxon matched pair signed-rank test). Data collected and then statistically analysed by using WPS Excel version 2021 and GraphPad Prism version 9 software.

Results: Total IPD patients were found to be 111 in the present study with a mean age of IPD patients as 61.85±7.20 years. Incidence of WO in the present study was found to be 40.5% among IPD patients. Most common characteristic of WO was found to be tremor in 104 (28.8%) patients followed by slowness of movement in 63 (17.5%) patients. WHO-UMC scale and Naranjo causality assesment scale both revealed 36.4% ADRs were probable category and 63.6% were possible category. MDS-UPDRS Score, PDQ-39 Score, MMAS-8 score significantly (p-value<0.05) improved during the course of treatment.

Conclusion: Dose adjustment of syndopa was mostly used in the management of WO phenomenon and significant improvement in the quality of life of the patients was seen.

Keywords: Co-morbidity, Life quality, Pathology, Synuclein, Tremors, Tolerability

INTRODUCTION

The PD is the 2nd most frequent neurodegenerative disease, affecting 1% of the population aged >60 years [1,2]. Neuropathological hallmarks of PD are striatal dopamine deficiency. PD characteristic features are bradykinesia, rigidity, rest tremor and Non Motor Symptoms (NMS) [3]. Dopamine replacement with oral levodopa is still the gold standard of symptomatic therapy [4]. Levodopa long-term use can lead to 'WO' or 'end of dose' deterioration [5]. WO management usually by levodopa, levodopa plus Carbidopa. Addition of other drugs like doßpamine agonist, anticholinergics, N-methyl-D-aspartate (NMDA) antagonist, Catechol-O-methyltransferase (COMT) inhibitor, Monoamine Oxidase type B (MAO-B) inhibitors may improve the symptoms [6-9]. Registry-based study can either be a clinical trials or non interventional study [10,11].

Registry-based study can be used to find out effectiveness, safety and tolerability, quality of life, adherence [12-14]. Aims of clinical pharmacology reconciliation are to check for valid clinical indication for each prescribed drug and to have a clear therapeutic goal and evidence base for each prescribed drug [15]. There are few studies conducted in India (Obering CD et al., Perepezko K et al., and Shah J et al.,) regarding treatment reconciliation in WO and no such similar studies in West Bengal, India [16-18]. Hence, the present study was designed to investigate the WO effects in patients of PD, their pharmacotherapy and outcomes in a Tertiary Care Hospital of West Bengal, India and private clinics of one practicing neurologist.

MATERIALS AND METHODS

This was a registry-based, prospective, observational, outcomes-based study conducted at the Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, West Bengal, India, in collaboration with Neuromedicine of Kolkata Medical College and private clinics of one consultant neurologist in Kolkata/suburban areas, West Bengal, India,

from January 2020 to December 2021. Study was conducted after approval by the Institutional Ethics Committee of School of Tropical Medicine, Kolkata (CREC STM/595) and Ethics Committee of Medical college and Hospital, Kolkata (MC/KOL/IEC/NON SPON/771/08/20). An attempt was also undertaken to make a registry of IPD patients.

Due to sudden demise of one renowned neurologist of Kalyani, West Bengal, India, authors excluded this private clinic and enrolled data from three private clinics of only one neurologist of Howrah, West Bengal, India. Subject enrollment was done six months, follow-up was done 12 months, data analysis and report writing was done for four months.

Inclusion criteria: Adult subjects of either sex, IPD cases duly diagnosed, attending neurology clinic regularly, receiving drug therapy for PD for atleast one year, patients willing to take part in the study, and consented to participate were included in the study.

Exclusion criteria: Those who had a history of WO and did not give informed consent were excluded from the study.

Study Procedure

Patients were enrolled from Neuromedicine OPD of Medical College and Hospital, Kolkata, as well as from private clinics of one neurologist in Howrah, West Bengal according to inclusion and exclusion criteria after taking the informed consent. Patient's data were filled in the Case Record Form (CRF) at baseline and then followed-up for three visits (at one month, three month and six month). The basic demographic details (age, sex), presenting complaints along with the medications history in a prestructured data collection form were noted. Cognitive assessment, rigidity, tremor according to MDS-UPDRS scale were assessed [16]. The MDS-UPDRS scale was developed for the assessmsent of various aspects of PD such as non motor and motor experiences of daily living and motor complications [16]. MDS-UPDRS scale comprises of four parts with the response bearing lower score than positive response using 5-point Likert scale. Those patients who developed WO in subsequent follow-ups were diagnosed by neurologists. Then patient's WO onset and duration, were observed and noted. WOQ19 Questionnaire used to screen for WO symptoms in patients with PD [17]. WOQ19 is a 19 items self-report measure to screen for end-of-dose (WO) symptoms in PD patients. Characteristics of WO among IPD patients, distribution of antiparkinsonian drugs among WO patients and co-morbidities among IPD patients were also observed.

Quality of life evaluated by PDQ-39 at baseline and three follow-up periods [18]. PDQ-39 is a 39-item self-report questionnaire, which assesses PD specific health related quality of life. Medication adherence was assessed by using Morisky medication adherence scale [19-25]. Medication adherence was assessed by MMAS-8 scale which is a structured self-reporting tool accepted globally.

In both of the scales negative responses had higher scores in comparison to positive responses and totaling into 11 and 195, respectively. PDQ-39 uses 5-point Likert scale whereas, MMAS-8 scale having score 1 with negative response. The study questionnaires and scales were administered in English mostly among the study subjects. In case of defaulters, authors have translated those forms and scales in local vernacular and presented before them after validating it with back translation. Safety of antiparkinsonian medications was analysed by monitoring suspected adverse drug reactions by using suspected ADR Reporting Form of Indian Pharmacopeia commission (version 1.3) [6,26]. Causality of such reactions were assessed using WHO-UMC Causality Assessment Scale, Naranjo's Algorithm [6,26]. Severity of the reactions were assessed using Hartwig and Seigel's Severity Assessment Scale [6,26]. Different parameters were recorded at baseline, 1st follow-up, 2nd follow-up and 3rd follow-up. (Permission was sought for using the Morisky's Adherence Scale and before International Parkinson and Movement Disorder Society for MDS-UPDRS scale and other questionnaires. Being a member of International Parkinson and Movement Disorder Society, the 1st author got the access of those questionnaires).

STATISTICAL ANALYSIS

Data was collected and then statistically analysed. Qualitative data was represented as frequencies and percentages. Quantitative data was presented as mean±SD or median and Interquartile range. The data was then analysed with parametric or non parametric tests using (Mean±SD, Median, Fisher's-exact test, Friedman's ANOVA test, Wilcoxon matched pair signed-rank test) using WPS Excel version 2021 and GraphPad prism version 9 software.

The data were entered into WPS Excel sheet and the master chart was taken as the patient registry.

RESULTS

Total IPD patients were found to be 111 in the present study. Incidence of WO in the present study found to be 45 (40.5%) among IPD patients and the mean age of IPD was 61.85±7.20 years in the present study. Median age of IPD was 62 years. A total of 27(60%) WO patients were in age group <65 years and a total of 18 (40%) WO patients were in age group ≥65 years. A total of 39 (86.7%) WO patients were found in males and a total of 6 (13.3%) WO patients were found in females.

Total WO developed among IPD patients (111) were 45 (40.5%) in the present study. [Table/Fig-1] depicts WO developed among Idiopathic Parkinson patients. At baseline there was no WO. The WO in 1st follow-up period was 16 (14.4%), in 2nd follow-up were 20 (18%) and in 3rd follow-up were 9 (8.1%). [Table/Fig-1] also depicts descriptive statistics of WO onset at baseline and follow-ups. At baseline, WO onset time mean and median both was 0. At 1st follow-up mean was 91.23 minutes and median was 85 minutes. At 2nd follow-up mean was 96 minutes and median was 100 minutes. At 3rd follow-up mean was 107.2 minutes and median was 120 minute. Only mean and median value evaluated for WO onset time in different follow-ups.

Visit	Baseline	1st follow-up	2nd follow-up	3rd follow-up
Wearing-off (WO) number, n (%)	0	16 (14.4%)	20 (18%)	9 (8.1%)
Wearing-Off (WO) onset time (Minute) Mean±SD	0	91.23±23.91	96±25.63	107.2±25.87
Wearing-Off (WO) onset time (Minute) Median	0	85	100	120

[Table/Fig-1]: Wearing-Off (WO) among Idiopathic Parkinson Disease (IPD) Patients (n=45).

[Table/Fig-2] depicts co-morbidities among IPD patients. Most common co-morbidities were hypertension 8 (33.3%) patients and diabetes mellitus type 2 (n=8, 33.3%). [Table/Fig-3] depicts characteristics of WO among the patients of IPD. Most common characteristic of WO was found to be tremor (n=104, 28.8%) followed by slowness of movement (n=63, 17.5%). The other motor complaints reported were difficulty in getting out of chair (13.6%), muscle cramping (4.4%) and general stiffness (2.5%).

Hypertension	Diabetes mellitus type 2	Hypothyroidism	Dyslipidemia	Smoker
8 (33.3%)	8 (33.3%)	4 (16.7%)	3 (12.5%)	1 (4.2%)

[Table/Fig-2]: Co-morbidities among Idiopathic Parkinson Disease (IPD) patients. Total co-morbidities=24; Values are presented as n (%)

Tremor	Slowness of movement	Weakness	Difficulty in getting out of chair	Difficulty in speech	Pain	Muscle cramping	Experiencing hot and cold	General stiffness
104 (28.8%)	63 (17.5%)	55 (15.2%)	49 (13.6%)	33 (9.1%)	17 (4.7%)	16 (4.4%)	15 (4.2%)	9 (2.5%)

[Table/Fig-3]: Characteristics of WO among the patients of Idiopathic Parkinson's Disease (IPD) (N=361).
Total clinical features=361; Values are presented as n (%)

Drugs with dose (mg)	Syndopa 110 mg	Trihexyphenidyl (THP) 2 mg	Pramipexole 0.5 mg	Ropinirole 0.25 mg	Amantadine 100 mg	Rasagiline 0.5 mg
WO No. of subjects	45 (100%)	22 (48.8%)	14 (31.1%)	11 (24.4%)	2 (4.4%)	2 (4.4%)

[Table/Fig-4]: Distribution of Antiparkinson's drugs among Wearing-off (WO) Patients (N=45).
Total WO patients=45; Values are presented as n (%)

Score	Baseline (Mean±SD)	1st follow-up (Mean±SD)	2nd follow-up (Mean±SD)	3rd follow-up (Mean±SD)	p-value (Friedman's ANOVA)
MDS-UPDRS	15.02±7.24*	13.68±6.82*	10.53±5.54*	7.40±4.13*	**p<0.001**
MMAS	7.15±0.91**	7.23±0.81	7.29±0.70**	7.53±0.58**	**p<0.05**
PDQ 39	180.7±6.35#	183.6±4.65#	188±4.26#	192.3±2.76#	**p<0.001**

[Table/Fig-5]: Different parameters at baseline and follow-ups (MDS-UPDRS, MMAS, PDQ-39 scales).
Post-hoc Analysis; Wilcoxon matched pair signed rank test
*p<0.001 in comparison to baseline and (1st, 2nd, 3rd follow-up, respectively), 1st follow-up and (2nd, 3rd follow-up, respectively), 2nd follow-up and 3rd, follow-up) in case of MDS-UPDRS.
**p<0.001 in comparison to baseline and 3rd follow-up, p<0.01 in comparison to 2nd follow-up and 3rd follow-up in case of MMAS.
#p<0.001 in comparison to baseline and (1st, 2nd, 3rd follow-up, respectively), 1st follow-up and (2nd, 3rd follow-up, respectively), 2nd follow-up and 3rd follow-up in case of PDQ 39 score

While chief non motor complaints were weakness (15.2%), dificuly in speech (9.1%), pain (4.7%), experiencing hot and cold (4.2%). [Table/Fig-4] shows the distribution of antiparkinson's drugs among WO patients. Syndopa mostly used alone or along with added drugs in patients to treat WO. Syndopa>Trihexyphenidyl (THP)>pramipexole>ropinirole>amantadine, rasagiline. Patients were treated by usual regimen antiparkinsonian drugs regimen. [Table/Fig-5] shows different parameters at baseline and follow-ups (MDS-UPDRS, MMAS, PDQ-39 scales).

[Table/Fig-6] depicts suspected drugs causing ADRs and their causality assessment by WHO-UMC scale and Naranjo causality assessment scale among IPD patients. WHO-UMC Scale and Naranjo causality assessment scale both revealed 36.4% ADRs were probable category and 63.6% were possible category. [Table/Fig-7] Shows Hartwig's severity scale, according to it 11 (100%) ADRs were in level 1 of mild intensity.

Suspected drugs	ADRs	ARDs n (%)	WHO-UMC Causality Assessment scale [26]	Naranjo Causality Assessment Scale [26]
THP	Dry mouth	4 (36.4%)	Probable	Probable
	Drowsiness	2 (18.1%)	Possible	Possible
Syndopa	Dizziness	4 (36.4%)	Possible	Possible
Syndopa	Nausea	1 (9.1%)	Possible	Possible

[Table/Fig-6]: ADRs in idiopathic parkinsonism patients (N=11) according to WHO-UMC causality assessment scale [26] and Naranjo causality assessment scale [26].
Total ADRs=11

Severity	Level	Number of ADRs	Total (%)
Mild	1	11	100%
	2	0	
Moderate	3	0	0
	4	0	
Severe	5	0	0
	6	0	
	7	0	

[Table/Fig-7]: ADRs according to Hartwig'S Severity Scale [26].

DISCUSSION

The present study was designed to assess WO onset and its pharmacotherapy, to evaluate patient's outcomes in terms of MDS-UPDRS score, safety and tolerability, medication adherence and quality of life and to explore treatment in emergency situations. Also, an attempt was made to form a registry of such patients, but due to Coronavirus Disease-2019 (COVID-19) it could not be completed. In the present study, the chief motor complaints were tremor (28.8%), slowness of movement (17.5%), difficulty in getting out of chair (13.6%), muscle cramping (4.4%), general stiffness (2.5%). while chief non motor complaints were weakness (15.2%), dificuly in speech (9.1%), pain (4.7%), experiencing hot and cold (4.2%). A study by Perepezko K et al., study revealed that the most common WO symptom was tremor (69.5%) [17].

In the present study, incidence of WO was found to be 40.5% among IPD patient which was nearly similar with Perepezko K et al., in which WO was 40% among IPD patients [17]. About 70 (63%) and 41 (37%) of IPD patients were in age group of <65 years and ≥65 years, respectively. In the present study, mean age was found to be 61.85±7.20 years corroborating with Shah J et al., where the mean age was 61.88±11.93 years [18].

Quality of life is an important measure for PD, in terms of physical and mental health outcomes. Quality of life in the present study was measured by using PDQ-39 Score. In the present study, authors evaluated quality of life by using PDQ-39 questionaire. Mean PDQ-39 score was found to be 180.7±6.35 at baseline that was found to be improved in follow-ups. In a study by Saha J et al., study , mean total PDQ-39 score was 130.45, nearly approximate to the present study [18]. Higher score indicates better quality of life. In the present study, WO in males was found to be 86.7% and in females 13.3%. Colombo D et al., revealed 61.9% WO in males which was higher than females (38.1%). Majority of studies also showed WO mostly in males [27]. In the present study, mean MDS-UPDRS score was found to be 15.02±7.24 which is nearly similar to Obering CD et al., with MDS-UPDRS score of 15.78±11.53 [16].

Antiparkinson's drugs are usually well tolerated and adverse events range from mild to moderate found in a study by Carbone F et al., [6]. Another study by Thaha F et al., also revealed that majority of ADRs in their study was mild in intensity [26]. In the present study, authors assessed safety and tolerability to antiparkinson's drugs and adverse drug reactions from patients complaint, physical examinations by neurologists. According to modified Hartwig's Severity scale, all the ADRs were mild in intensity as no drug withdrawal or no drug modification needed to treat the ADRs.

This showed the improvement of adherence from baseline to further follow-ups. It also revealed improvement of quality of life from baseline to further follow-up visits. Multiple drugs are now available to treat IPD patients such as levodopa plus carbidopa combination, dopamine agonists like ropinirole, pramipexole, bromocriptine, cabergoline, apomorphine, MAO-B inhibitors like selegiline, rasagiline, NMDA antagonist like amantadine, other drugs like safinamide, rotigotine etc., [28]. The effectiveness of these drugs can be evaluated by using MDS-UPDRS score of international movement disorder society. In the present study, authors evaluated effectiveness of antiparkinson drugs by using MDS-UPDRS score in follow-ups.

Shah J et al., study revealed the effectiveness of antiparkinson medications by using MDS-UPDRS score [18]. WHO-UMC scale showed 7 (63.6%) cases in possible category and 4 (36.4%) cases in probable category, Naranjo scale showed 7 (63.6%) cases in possible category and 4 (36.4%) cases in probable category.

Thaha F et al., study revealed that 72.5% ADRs were found to be possible category and 27.5% were found to be in unlikely category [26]. Hartwig's Severity scale showed 11 (100%) cases were of mild in intensity. Thaha F et al., revealed that majority of ADRs in their study were mild in intensity that was nearly similar to the present study [26]. Medication adherence is an important parameter to assess the quality of life and it's improvement. In the present study, authors evaluated medication adherence by using MMAS score. Mean MMAS score was found to be 7.15±0.91 at baseline and was also improved as follow-ups progressed [19]. Clinical pharmacological reconciliation was very important for improving medication adherence and quality of life [29]. In the present study, all patients have good adherence except few, who are poorly adherent to drugs, that might be due to COVID-19 pandemic and economic background of such patients.

Limitation(s)

Patients were followed-up for a period of six months due to the COVID-19 pandemic which is a very short duration to evaluate the outcomes and maintenance of registry. Entire spectrum of the disease and quality of life correlation could not be done. Because of time constraint other parkinson's tools could not be used and as the present study is registry-based study it was difficult to do this type of study in short period. Authors attempt to make a complete patient registry has been interrupted due to COVID-19 pandemic and work is ongoing.

CONCLUSION(S)

In the present study, syndopa was mostly associated with WO phenomenon. Overall, antiparkinson drugs were safe, well tolerated and effective in the management of WO phenomenon. Moreover, dose adjustment of syndopa or addition of newer drugs helped in significant improvement in quality of life. Additional treatment reconciliation service by clinical pharmacologist can improve the medication adherence, quality of life and therapeutic outcome among PD patients.

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