Factors Affecting Adherence to Pharmacotherapy in Parkinson's Disease

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Abstract

Background: The goal of dopaminergic replacement therapy to achieve good clinical outcome in Parkinson's disease (PD) patients largely depends on the pattern of adherence to the pharmacological treatment. This study aims to find the factors affecting medication adherence in patients with PD keeping in mind the cultural, economic, and social diversities so that preventive steps can be taken to fill these gaps. **Methods:** Demographic data, disease parameters, treatment-related factors, family characteristics, educational, and employment status were assessed for relationship with the medication adherence pattern in a cohort of non-demented PD patients. Medication adherence was measured by MMAS-8; depression, and socioeconomic status were assessed by GDS-SF and Kuppuswamy scales respectively. **Results:** From 134 PD subjects, high adherence was observed in 43.2%, 18.2% had moderate, and 38.6% reported low adherence level to their pharmacotherapy. The sub-optimal level of adherence was significantly correlated to compliance of follow up with the physician (p 0.03), presence of adverse events related to drugs (p 0.03), and depressive symptoms (p < 0.0001). Also, there was significant negative co-relationship between poor adherence and depression on Spearman's rank coefficient (0.702). There was no effect of demographic factors, living conditions, family type, educational qualification, associated comorbid conditions, and socioeconomic status on adherence to dopaminergic treatment in patients with PD. **Conclusion:** Poor adherence to prescribed medication is a menace that is more than just oversimplification of forgetfulness which should be evaluated at each visit to improve efficacy of the prescribed regimen to achieve better treatment result and thus quality of life of PD patients.

Keywords: Adherence, compliance, depression, Parkinson's disease, socioeconomic status

INTRODUCTION

Oral medications are the gold standard for treatment of Parkinson's disease (PD).[1] As with many other chronic conditions, the response to pharmacotherapy depends not only on the efficacy and appropriateness of the therapeutic regimen but also on the patient's adherence to the prescription. According to WHO, adherence to pharmacotherapy means "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."[2] Physicians interpret the lack of response as disease progression leading to unnecessary treatment changes which sets up vicious cycle of suboptimal adherence[3] and predisposes to more levodopa fluctuations[4,5] that itself contributes to nonadherence.

There are gaps in the literature regarding the various factors affecting medication adherence.[6-9] Among the various factors that affects drug adherence, there is some evidence that longer disease duration[6,8,9] affects adherence patterns while others highlight that patient's mental status and depression are important determinants of adherence.[6,7,9] However, there has been a lack of data on medication adherence in resource limited and developing countries. India is a vast country with diverse demography features which are entirely different from that of the developed world. Therefore, it was imperative that a study be conducted for medication adherence keeping in mind the cultural, economic, and social background of the population.

MATERIALS AND METHODS

Participants

This was a hospital based observational cross-sectional study conducted at neurology department of a tertiary care hospital in India after obtaining clearance from the Institutional Ethics Committee (IEC No. 2019-402). Written informed consent was obtained from all patients. Patients clinically diagnosed with idiopathic Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank criteria,[10] on dopaminergic therapy with levodopa and/or dopamine agonist in minimum twice daily dose for a minimum of one year, with no changes in their dopaminergic therapy for last one month and responsible

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for maintaining their own daily medication were included in the study. Patients with cognitive dysfunction,[11] on antidepressant therapy, secondary Parkinsonism (multiple system atrophy, progressive supranuclear palsy, vascular PD) were excluded.

Methods

Demographic data including age of the patient, gender, comorbid illness such as diabetes mellitus, hypertension, coronary artery disease, and chronic disease in the family, family characteristics (type of family, living with life partner) was recorded. Educational qualification, rural/urban residence, employment status, and monthly income of the family were noted for assessing the socioeconomic status of the patient as per the Kuppuswamy scale, 2017.[12]

Disease factors such as age of onset of disease, duration of disease, severity (Hoehn and Yahr stage)[13] and Unified Parkinson's Disease Rating Scale – III (UPDRS-III) were also recorded in a pre-structured proforma.

Detailed treatment history including number, type of medication (levodopa, dopamine agonists, MAO inhibitors or COMT inhibitors), total pill burden and levodopa equivalent daily dose (LEDD) were also noted. Adverse drug events (ADEs) were also assessed using a structured questionnaire.[14] According to WHO, ADEs are medical occurrences temporally associated with the use of a medicinal product, but not necessarily causally related.[15] Compliance for hospital visit (neurology OPD) was classified as regular or irregular among the included PD patients. Patients who missed ≤ 3 scheduled follow up outpatient visits were classified as regular follow up and those who missed >3 scheduled follow up outpatient visits over one year were classified as irregular follow up patients. Patients visiting the OPD prior to their appointment were also considered as follow up visit; however, patients who missed their follow up visits due to Covid-19 pandemic were not classified as having irregular follow up.

Geriatric Depression Scale-Short form (GDS-SF) is a screening scale for identifying depression in PD patients and is recommended by Movement Disorder Society. This is a 15-item questionnaire as "yes/no" with respect to the experience of their symptoms. The answers that indicate depression are scored "1" each and a score of more than 5 is considered of having depression.[16]

Adherence assessment

Medication adherence was measured by the 8-item Morisky Medication Adherence Scale (MMAS-8).[17] This is a structured, self-report measure that provides information relating to patient behavior in context of medication use – unintentional (forgetfulness) or intentional (not taking medication due to side effects). The scale comprises 8 questions – seven of which have dichotomous "Yes/No" response choices while the last is scored on a five-point Likert type scale. Questions are formulated in such a way that it eliminates "yes-saying" bias. For item 8, score is given as 0-4 (Likert type) and

then divided by 4 for standardization of the code. The scale categorizes the patient adherence into three categories: high adherence (MMAS-8 score 0), medium (MMAS-8 score 1 or 2) and low adherence (MMAS-8 score >2).[17] The questionnaire was administered by the physician to all the patients.

Statistical analysis

Statistical analysis was done with the help of IBM SPSS Statistics 26. Demographic and clinical parameters were analyzed using descriptive statistics: means, standard deviations, percentages, and frequencies. The range and median of H & Y stages were calculated. Categorical variables including gender, rural/urban residence, regular/irregular follow up, adverse events to treatment, living with a life partner, comorbidity, chronic disease in the family, and socioeconomic status were analyzed with Chi-square. Quantitative variables including age, duration of disease, UPDRS – III score, pill burden, LEDD, and GDS-SF were analyzed using ANOVA test. Univariate analysis was first done with all the parameters associated with adherence using Chi-square test, ANOVA, and t-tests. Multiple regression analysis was then performed to find out the independent predictors of adherence. Spearman's rank correlation coefficient was used to measure the strength of correlation between the independent predictors of adherence (significant on multivariate analysis) and adherence pattern (MMAS-8). The level of statistical significance for all the tests was set at ≤ 0.05.

RESULTS

Of the 147 patients that meet the inclusion criteria, 10.2% (n = 15) patients were excluded. They were found to have history of overuse of dopaminergic drugs (behavioral impulse control disorder), although they can also be categorized as non-adherent as per WHO criteria. Out of the remaining 132 patients, 58.3% (n = 77) were males and 41.7% (n = 55) were females, with a mean age of 61.1 ± 10.3 years and a mean duration of illness of 4.5 ± 3.3 years. The severity on the H & Y stage ranged from 1-4 with a median of 2 and with mean UPDRS-III score of 58.3 ± 12.9. In the current study, 94.7% (n = 125) patients were prescribed levodopa therapy with or without other dopaminergic drugs while 32.6% (n = 43) patients were taking at least one dopamine agonist and mean LEDD was 433.3 ± 187.1 mg. Sixty-one patients (46.2%) had less than ten years of education (illiterate/primary school/middle school), 39.4% (n = 52) were educated till high school, and 14.4% (n = 19) had graduate/post graduate degree. There were 66.7% (n = 88) patients who were not working/retired, 24.2% (n = 32) were semi-skilled, and 0.1% (n = 12) were professionals/semi-professionals. Other detailed clinical, demographic, disease, and socioeconomic characteristics are presented in the Table 1.

With regard to adherence, 43.2% patients (n = 57) reported high level of adherence, 18.2% patients (n = 24) had medium level of adherence while 38.6% patients (n = 51) had low level of adherence, as depicted in Figure 1.

On univariate analysis, of various factors that could influence adherence pattern there was significant association of adherence

level with hospital follow up visits, as patients who had irregular follow up with their physician had poor compliance (p = 0.03). In addition, presence of ADEs related to treatment (p = 0.03) and depressive symptoms (p < 0.0001) were also significantly

Table 1: Demographic, clinical factors, family characteristic and socioeconomic status of cohort of 132 PD patients*

Characteristics		All participants
Age (years)		61.1 (10.3)
Duration (years)		4.5 (3.3)
Severity (H&Y)		2 (1-4)
UPDRS-III		58.3 (12.9)
LEDD		433.3 (187.1)
Pill burden		6.1 (3.5)
GDS-SF		6 (3.9)
Gender	Females	55 (41.7)
	Males	77 (58.3)
Rural/Urban	Rural	48 (36.4)
	Urban	84 (63.6)
Regular follow up	No	63 (47.7)
	Yes	69 (52.3)
ADEs	No	58 (43.9)
	Yes	74 (56.1)
Life partner	No	27 (20.5)
	Yes	105 (79.5)
Any other family member with chronic disease	No	107 (81.1)
	Yes	25 (18.9)
Socioeconomic class	Upper	102 (77.3)
	Middle	27 (20.4)
	Lower	3 (2.3)
Associated comorbidity	No	80 (60.6)
	Yes	52 (39.4)

*Numerical variables were expressed as mean (standard deviation); categorical variables were presented as n (%); H&Y was presented as median (range). H&Y; Hoehn & Yahr stage; UPDRS-III, Unified Parkinson's disease Rating Scale-part III: motor examination; LEDD, Levodopa equivalent daily dose (mg); GDS-SF, Geriatric Depression Scale-Short Form; ADEs, Adverse drug events
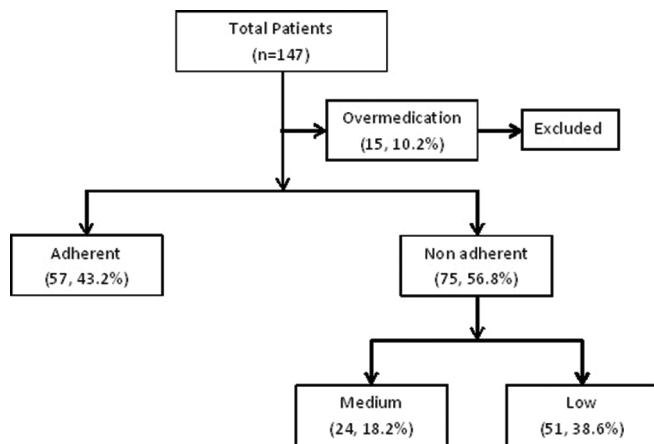
associated with presence of poor adherence among the PD cohort [Table 2]. On multiple regression analysis, depression was the strongest and independent predictor (p < 0.0001) of poor adherence in this study. Further there was also significant correlation (p < 0.0001) of depression and adherence pattern with Spearman's rank coefficient of 0.702. Scatter plot shows that as the medication adherence decreases, the severity of depression increases and vice versa revealing a direct, linear, and negative co-relationship between poor adherence and depression [Figure 2].

We did not find any effect of demographic factors (age, gender, educational qualification, employment status) on the adherence pattern. There were no significant differences in disease factors (duration of disease, UPDRS-III, LEDD, and pill burden) between the groups of high, medium, and low adherence patients in our cohort. Other factors like socioeconomic status, rural/urban residence, living with life partner, comorbid illnesses, and chronic illness in the family also had no significant association with adherence to medication.

DISCUSSION

Various studies in literature suggest nonadherence to medication as a major issue in clinical management of PD patients. This has several ramifications including higher readmission rates and reduced quality of life.[6,8] Also, it represents a financial burden to the health system and reduces the benefit of pharmacotherapy.[18] We aimed to use a multimodal approach and wider perspective to study all the factors affecting medication adherence and try to bring forward any relationship, if any exists, between such diverse factors and medication adherence. This study comprehensively studies the demographic, socioeconomic, caregiver, and medication related factors affecting adherence pattern in a cohort of PD patients. This cohort reveals high adherence among 43.2%, medium adherence among 18.2%, and low adherence among 38.6% on MMAS-8. Studies conducted in the developed regions of the world have demonstrated variable patterns
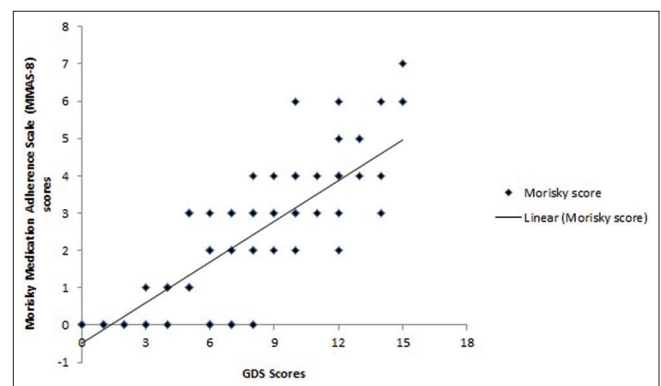

Figure 1: Flowchart of patients included in study with their adherence pattern

Figure 2: Scatter plot showing correlation of MMAS-8 and GDS-SF with spearman's rank coefficient (0.702)

Table 2: Comparison of characteristics according to adherence pattern*		High adherence *n*=57	Medium adherence *n*=24	Low adherence *n*=51	*p*
Characteristics					
Age (years)		61.5 (10.3)	63.5 (10.7)	59.5 (10)	0.267
Duration (years)		4.6 (3.1)	4.5 (3.1)	4.3 (3.8)	0.94
Severity (H&Y)		2 (1-4)	2 (1-4)	2 (1-4)	0.541
UPDRS-III		58.6 (12.5)	62.6 (13.3)	55.8 (12.9)	0.105
LEDD		453.5 (235.1)	437.3 (161.4)	408.8 (132.1)	0.467
Pill burden		6.3 (3.9)	5.6 (2.7)	5.9 (3.3)	0.676
GDS-SF		3.3 (2.8)	6 (2.2)	9 (3.4)	**<0.0001**
Gender	Females	25 (43.9)	7 (29.2)	23 (45.1)	0.386
	Males	32 (56.1)	17 (70.8)	28 (54.9)	
Rural/Urban	Rural	19 (33.3)	7 (29.2)	22 (43.1)	0.191
	Urban	38 (66.7)	17 (70.8)	29 (56.9)	
Regular follow up	No	20 (35.1)	12 (50)	31 (60.8)	**0.028**
	Yes	37 (64.9)	12 (50)	20 (39.2)	
ADEs	No	30 (52.6)	9 (37.5)	16 (31.4)	**0.032**
	Yes	27 (47.4)	15 (62.5)	35 (68.6)	
Life partner	No	12 (21.1)	7 (29.2)	8 (15.7)	0.398
	Yes	45 (78.9)	17 (70.8)	43 (84.3)	
Any other family member with chronic disease	No	49 (86)	18 (75)	40 (78.4)	0.428
	Yes	8 (14)	6 (25)	11 (21.6)	
Socioeconomic class	Upper	47 (82.5)	21 (87.5)	34 (66.7)	0.212
	Middle	9 (15.8)	3 (12.5)	15 (29.4)	
	Lower	1 (1.7)	0	2 (3.9)	
Associated comorbidity	No	33 (57.9)	12 (50)	35 (68.6)	0.262
	Yes	24 (42.1)	12 (50)	16 (31.4)	

*Numerical variables were expressed as mean (standard deviation); categorical variables were presented as n (%); H&Y was presented as median (range). H&Y; Hoehn & Yahr stage; UPDRS-III, Unified Parkinson's disease Rating Scale-part III: motor examination; LEDD, Levodopa equivalent daily dose (mg); GDS-SF, Geriatric Depression Scale-Short Form; ADEs, Adverse drug events. Bold is used to highlight statistical significance

of adherence.[6,8] In a review conducted by Malek *et al.*,[19] noncompliance varied between 10-67%. We studied the factors responsible for such variation in adherence pattern. This may provide a possibility of converting medium adherence category group to high adherence group by modifying the factors affecting the medium and low adherence groups. Although 100% adherence seems hypothetical but improving adherence level to beyond 60/70% in any chronic disease such as PD may change the outcome of the patients.

There exist a variety of methods for the measurement of adherence. WHO categorizes these methods as subjective, which involve patients' own perception of their adherence (self-reports); and objective, when the health care provider measures the adherence. MMAS-8 is a subjective self-reported brief questionnaire and has been validated in many previous studies. It is moderately correlated with pill count and is more sensitive for detecting nonadherence.[20] Pill counts, electronic monitoring and prescription records are objective methods that are although accurate for determining compliance but the patients may just discard medication and return empty bottle.[21] Electronic methods are expensive; hence restricting their use in resource limited settings. Measurement of drug or metabolite levels of levodopa is not possible in clinical practice.

On analysis, it was found that presence of ADEs had significant association with the adherence pattern (p = 0.03). This reveals the fact that when a PD patient experiences ADE, they will either reduce their medication or stop it altogether. This not only reduces the adherence but also negatively impacts the faith[22] in the effectiveness of treatment, indirectly influencing their compliance of follow up. PD being a progressive neurodegenerative disorder; once patients become non-compliant there occurs worsening of motor disability setting a vicious cycle thus implying a cause-and-effect relationship of ADEs with medication adherence. Presence of ADEs exemplifies one of the most significant barriers for patients' medication behavior which is also seen in other chronic disorders.[23,24] Other medication related factors like LEDD and pill burden showed no significant association to the adherence in this study.

In this study, compliance of regular follow up with the physician was another significant factor affecting adherence in this PD cohort. Patients who had poor adherence were found to be on irregular follow up; this factor has never been explored in previous studies although experienced by many physicians in their usual practice. We hypothesize that regular follow up plays an important role in modifying patients' behavior. ADEs and irregular follow up are mutually inclusive of each

other. Hence, it is important to assess both factors in PD patients for their adherence. Multivariate analysis highlights the confounding effect of both these factors as only depression was found to be independent predictor of poor adherence. Thus, one's behavior might be interfering with the motivation to visit their physician and also to take their prescribed pills regularly. When a patient visits their physician, the physician has the opportunity to influence their adherence pattern. Knowledge about the disease imparted during each follow up visit goes a long way in shaping up the patients' behavior. Patients with good knowledge of their disease, its severity, adverse events from treatment and prognosis of the disease help them to adhere more to their treatment than their ignorant counterparts.[7,22] So this is a potential area calling for intervention to improve the efficacy of the prescribed regimen. Regular follow up should be encouraged with the PD patients and their caregivers to improve the treatment and quality of life.

With regards to disease related factors, there was no association seen between severity (H&Y stage, UPDRS-III score) and duration of disease and adherence pattern. Most of the patients know about the chronic nature of disease. Although adherence may be poor but patients usually have a tendency to take their prescribed medication before visiting their physician. This puts them in the "on" phase likely explaining the no significant association between disease related factors and adherence pattern in this cohort. In early stages of PD (H&Y stage of 1-2), intermittent skipping of doses does not lead to a large deterioration in motor score (UPDRS-III). Median H&Y stage in our cohort was 2 and this might be the reason that there was no significant association between disease severity and adherence.

Our study elaborates a strong negative correlation [Figure 2] between depression and poor adherence. Grosset *et al.*[6] and Valldeoriola *et al.*[7] reported poor adherence to pharmacotherapy in PD patients with depression. Our study echoes similar results demonstrating mean GDS-SF score of 9 ± 3.4 in low adherence group (p < 0.0001). Reduced energy, feelings of worthlessness and indecisiveness creates more negative expectations from the treatment outcomes,[25] giving rise to a vicious circle wherein depression contributes to nonadherence to pharmacotherapy and consequently, worsening symptoms leads to more depressive symptoms.[25,26] Assessing depression and adherence together is therefore relevant to the management of PD and is recommended to improve their outcome. Although the association between depression and adherence is evident in our study, we did not explore whether treating depression would improve adherence, this requires specific studies to answer.

We studied the differences in patterns of adherence among different age groups and genders. Absence of any significant difference among different age groups or gender in this study compared to previous studies suggests that taking medication was a priority. Living in rural/urban area had not shown any significant differences in the context of the adherence patterns highlighting that resources are available to the people living in

rural area for their disease provided they are motivated to take them. Similarly, socioeconomic status of the family, education, qualification, as well as employment status of PD patients was not significantly different among the different adherence groups. This is in sharp contrast to the studies conducted in the resource rich developed regions of the world where significant association of medication adherence was seen with education status, income, and employment status. Study from Spain by Leopold *et al.*[27] reported poor adherence with <16 years of education. But in our study, there was no difference with regard to education status indicating that if patients are made to understand their disease and medication, it affects medication adherence irrespective of education status. Banks and Lawrence reported that patients are more adherent to their therapy if they are employed as dopaminergic drugs enable them to get through their working hours.[28] In our cohort 66.7% patients are unemployed which may be reason for higher incidence of nonadherence.

This study brings forth that presence or absence of life partner of PD patient did not influence the adherence pattern although Valldeoriola *et al.*[7] found good adherence in people living with their spouses. This difference may be culturally related as 79.5% of PD patients in this cohort lived in joint families in contrast to the developed countries where living in nuclear families is preferred.[29] Additionally presence of chronic illness in only 18.9% the families of this cohort make the PD patient more adherent because family members were engaged in the therapeutic process.

In this study, we looked at the wider range of predictors for adherence; demographic factors (age, gender, residence, education, employment), disease related factors (severity), medication related factors (adverse events, pill burden, regular/irregular follow up), and socioeconomic factors (spouse, chronic disease in the family, socio-economic status, comorbidity, depression). PD patients adhered to their medication regimen regardless of the effect of any of these factors provided they were not depressed and had good compliance in their follow up with the physician. There are conflicting results in literature that level of adherence also correlates with other factors such as complexity of therapeutic schedule mood disorders[6,26] and non-motor symptoms (constipation, anxiety and psychosis)[30] which needs to be addressed and explored in future studies. Good communication with the patient and the caregiver, and addressing their queries regarding disease and medication related adverse events are essential steps in improving adherence in neurodegenerative disorder like PD. In this regard PD nurse and clinical pharmacist can be the bridge of communication between the physicians and PD patients in further improving medication adherence.

This study is not free of limitations. Although questionnaire method was used to measure adherence, it can still overestimate adherence[31] and can be a source of recall bias if patients return to follow up after a long time. Additionally, objective methods like electronic monitoring can be incorporated in future assessments along with subjective assessment tools to find out

the accurate estimation of incidence of adherence among the PD patients.

Summary

Taking less medication than prescribed is a menace that is more than just oversimplification of forgetfulness or adverse effects. It encompasses complex patient behavior and still has a lot to be known. Depression is the paramount factor affecting adherence and calls for screening especially in the elderly PD patients. Medication adherence should be evaluated at each clinic visit especially before modifying the treatment.

Conflicts of interest

There are no conflicts of interest.

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